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# Quarterly Review of MEDICINE

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INTERNATIONAL RECORD OF MEDICINE

The Present Status of Anticoagulant Therapy in Acute Myocardial Infarction

*Burton L. Zohman and Henry I. Russek*

VOLUME 9 NO. 1 FEBRUARY 1952

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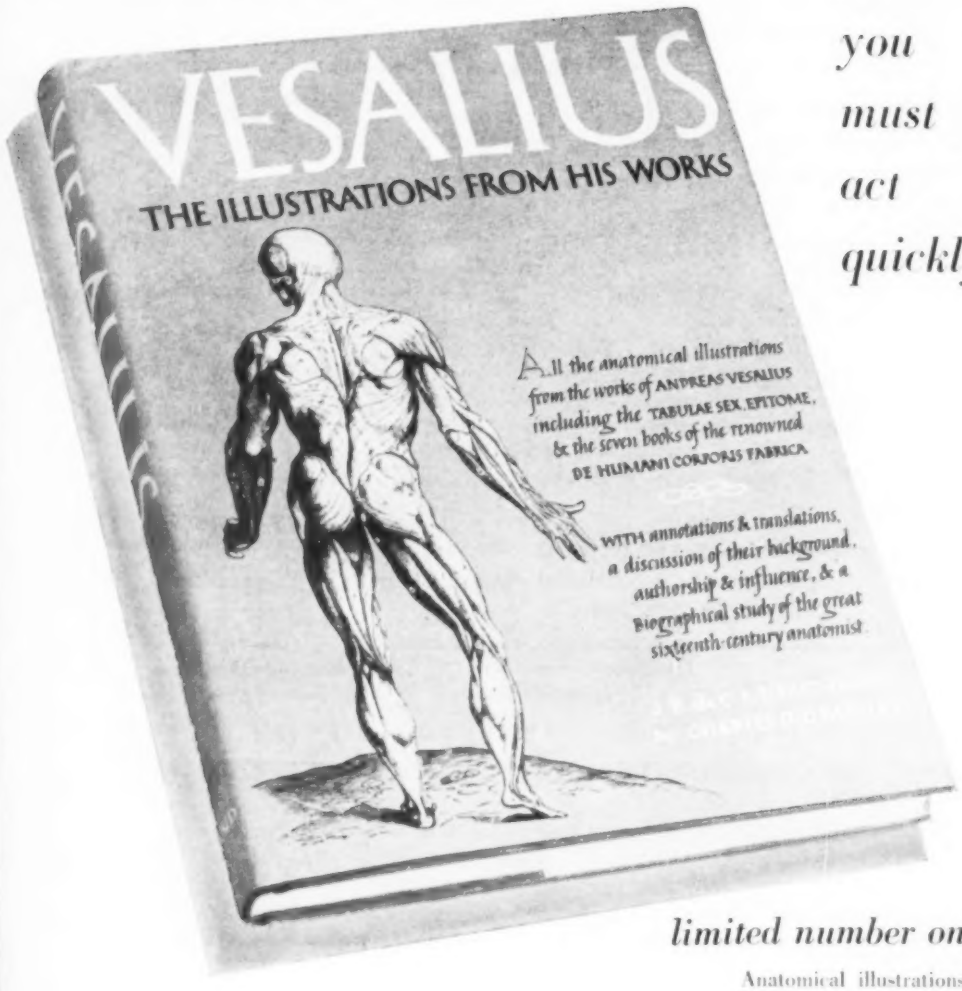


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# *Quarterly Review of* MEDICINE

**VOLUME 9 NO. 1** **FEBRUARY 1952**

*Incorporating the International Record of Medicine*


## INTERNATIONAL RECORD OF MEDICINE



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### *Infectious Diseases*



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**BOOK REVIEWS**

*Quarterly Review of* **MEDICINE**

**VOLUME 9 NO. 1** **FEBRUARY 1952**

*Incorporating the International Record of Medicine*

# The Present Status of Anticoagulant Therapy in Acute Myocardial Infarction*

*Burton L. Zohman, M.D., F.A.C.P.*†
BROOKLYN, N. Y.
*and*
*Henry I. Russek, M.D., F.A.C.P.***
STATEN ISLAND, N. Y.

The use of anticoagulants in the prevention and treatment of acute myocardial infarction was suggested by Best and his coworkers[1, 2] in a report on a series of animal experiments in which they demonstrated that the incidence of artificially induced intravascular clots could be lowered dramatically by the use of heparin. In 1938 Solandt and Best[3] produced coronary thrombosis regularly in experimental animals by injecting a solution of sodium ricinoleate into an isolated coronary artery. When the animals were heparinized prior to injection, thrombus formation was a rare occurrence. In 1939 Solandt, Nassim and Best[4] reported that the prior administration of heparin consistently prevented the development of large mural thrombi in the left ventricles of experimental animals in which the anterior descending branch of the left coronary artery was ligated and the subendocardial myocardium was injected with sodium ricinoleate.

Heparin or dicumarol was used clinically in individual cases, or in small series of cases of acute myocardial infarction during 1941 and 1942. The first American report concerned exclusively with the use of Dicumarol in acute coronary occlusion appeared in December 1945, when Wright[5] described his experience with 76 patients. Between the time of that report and 1949, over 20 individual series of cases were published in the American literature.

*Presented before the Combined Clinics of the Maimonides Hospital of Brooklyn, New York, on November 9, 1951.

†Attending Physician, Maimonides Hospital and State University Division of Kings County Hospital at Brooklyn, New York City; Cardiologist at Brooklyn State Hospital, New York City; Consulting Cardiologist, U. S. Public Health Service Hospital, Staten Island, New York.
**Consulting Physician in Cardiovascular Disease and Cardiovascular Research, U. S. Public Health Service Hospital, Staten Island, New York; Associate Cardiologist, Sea View Hospital, Staten Island, New York.

As reflected in these reports, the greatest experience with this means of therapy was obtained by Peters, Guyther and Brambel[6, 7] in Baltimore, by Nichol[8–10] in Miami, by Parker and Barker[11, 12] at the Mayo Clinic and by Wright and associates[13–17] in New York. Although the early reports seemed consistently favorable, the results were in no instance based upon a sufficiently large series of properly controlled cases to warrant statistical analysis. These initial observations did, however, lead to the more extensive study carried out by the American Heart Association's Committee for the evaluation of anticoagulants in the treatment of coronary occlusion with myocardial infarction.

This large scale investigation[18, 19, 19] at 16 leading hospital centers, provided data for statistical analysis of 1,031 cases of acute myocardial infarction. Of this number, 442 received conventional treatment for coronary thrombosis with myocardial infarction while 589 received heparin or dicumarol or both. The majority of this latter group received dicumarol alone; 15.6 per cent received both heparin and dicumarol. The composition of the sample as to age, sex, and previous history, was stated to be remarkably similar in the two groups. Of those patients not receiving anticoagulant therapy, 23.4 per cent died as compared to a mortality of 16.0 per cent in the group receiving this form of treatment. It appeared from these findings that approximately one-third of the expected deaths was prevented by the administration of anticoagulant drugs. Similarly, when the percentage of cases developing thromboembolic complications was examined, it was found that in the control group 26.0 per cent developed one or more of these complications as compared with 10.9 per cent in the treated group. Among the patients who suffered a recognized thromboembolic complication, 9.8 per cent of the control subjects died while 3.8 per cent of those treated died. The greatest benefits in the reduction of mortality were in patients 60 years of age or over. The crude death rates for patients less than 60 in both the treated and control groups did not show a significant difference, but the incidence of thromboembolic complications was markedly lower in the treated group. Wright[19] has emphasized that such nonfatal complications cannot be regarded lightly since they leave some patients hopeless hemiplegics, others with a loss of one or more limbs by amputation or with similar serious disabilities.

From these observations, the Committee concluded that anticoagulants should be administered to every patient suffering from an acute coronary thrombosis unless definite contraindications are present. In the absence of hemorrhagic conditions, the hazards from hemorrhage were not considered sufficient to contraindicate the use of anticoagulants in coronary occlusion provided that facilities for adequate laboratory and clinical control were available. The following conditions associated with myocardial infarction were the most important enumerated as contraindications for the use of dicumarol: (1) Severe hypertension, especially if the patient has a history of cerebral vascular accidents. (2) Bleeding from any cause, purpura of any kind, ulcerative lesions of the gastrointestinal tract. (3) Jaundice, hepatic cirrhosis, enlargement of the liver, impaired hepatic or renal function.

Independent studies reported in medical literature throughout the world have, for the most part, confirmed the observations and conclusions of the Committee sponsored by the American Heart Association. The careful studies of Tulloch and Gilchrist[20] at the Royal Infirmary in Edinburgh, Scotland, in which 70 patients treated with anticoagulants were compared with 84 control subjects, led them to conclude that dicumarol or related

drugs reduced by half the mortality rate during the first six weeks after myocardial infarction. In their experience, thromboembolic complications also seemed similarly reduced, and when they did occur, fatalities were lessened. These conclusions, although derived from a relatively small series of cases, are based on careful and well presented work in which the controls appear to fulfill most requirements. Some authors,[21, 22] however, have pointed out the difficulties in collecting a series of untreated controls which are truly comparable to a treated series. The prognosis in acute myocardial infarction is influenced by many factors among which are age, sex, previous angina pectoris or infarction, shock, congestive heart failure, arrhythmias and unrelated diseases. The difficulty in determining the prognosis after acute myocardial infarction is clearly indicated by reports presenting crude mortality rates varying from eight to 78 per cent. Some[22] have lucidly presented the pitfalls in attempting to interpret such an apparently sound fact as mortality rate. It is well known that the death rate in any series of hospital cases is markedly influenced by the number of admissions within the first 24 hours of the attack. The series reported by Yater,[23–25] for example, showed a mortality rate of 50 per cent in 866 male patients under 40 years of age. More than half of the fatal cases died within two hours of the attack. If all the immediate survivors had been sent to the hospital, the mortality rate calculated by the hospital staff could not have exceeded 30 per cent. Moreover, 18 per cent of the surviving group would have died within 24 hours and only 12 per cent thereafter, during the period of the acute illness. This simple analysis demonstrates that crude mortality figures mean little unless details are known. It indicates the difficulty in obtaining sufficiently well controlled case material to evaluate the effect on mortality of any form of treatment in this disease. Immediate admission to the hospital was almost certainly uncommon in the series of Wright and his associates. Otherwise, the mortality rate in the first week would have been appreciably higher than that in the second, whereas they were practically the same. It is possible that the figures presented by Wright and his group would have been even more impressive if a greater proportion of their patients had been seen and treated on the first day of their attack.

A few observers have reported no significant difference in mortality between patients who received dicumarol and those who did not. In most instances, the reported series were relatively small. Some authors believe that the rather impressive favorable statistics reported in the literature may have been due to effective suggestive therapy which accompanied the medical attention given to all patients receiving anticoagulant therapy. One observer has commented that control subjects in such studies are often almost completely neglected even to the point of being deprived of essential nursing care. The statistical data concerned with the incidence of thromboembolic complications in the series of Wright and associates has also been an object of critical analysis. These observers reported the incidence of thromboembolic manifestations in their control group to be 25.0 per cent, a figure in sharp contrast to the incidence of 11.5 per cent reported in the literature by others.[26] In recent years, however, a much higher clinical incidence for thromboembolic phenomena after coronary occlusion has been recorded suggesting that in earlier reports minor episodes had been overlooked.

In spite of these "disturbing features," there appears to be ample evidence that anticoagulant therapy merits an important place in the management of acute myocardial in-

farction. Even if available, statistics cannot be accepted at their face value, they certainly cannot be disregarded. It is reasonable, however, to demand convincing proof, for anticoagulant therapy is both a costly and troublesome procedure. Moreover, there are the dangers inherent in any interference with blood clotting: bleeding into the tissues generally, into the wall of the atheromatous coronary artery, and into the cardiac infarct itself with perhaps an increased risk of ventricular rupture. Aggravation of the cardiac lesion has not been observed in animal experiments, and, thus far, rupture of the ventricle has not been shown to be more common in patients treated with anticoagulants. Blumgart and his co-workers[27, 28] demonstrated that dicumarol produces no adverse effect on the myocardium of dogs which might retard the healing or development of collateral circulation in experimentally produced myocardial infarction. It has not yet been demonstrated whether anticoagulants increase the frequency of occlusion of coronary vessels by hemorrhage into the coronary wall. These considerations would be of no practical significance, however, if it could be shown from adequate and sufficiently controlled clinical material that anticoagulants have a beneficial effect in all cases of acute myocardial infarction.

In the light of present evidence, it is by no means certain that anticoagulant drugs should be used as a routine for all cases with this disease. Many physicians in general practice, as well as specialists in internal medicine or cardiovascular disease, do feel obliged to use an anticoagulant drug in every patient who sustains an attack of acute myocardial infarction. In some instances this attitide is doubtless based on a firm personal conviction regarding the value of this form of treatment. In others, it takes origin from the authoritative pronouncement of the American Heart Association's Committee that all cases should be treated in this manner. Many physicians who remain unconvinced or uncertain regarding the benefits to be derived from anticoagulant drugs continue their routine use chiefly because of fear of criticism by colleagues or of reproach by patients or their relatives who have been enlightened by medical articles in the lay press. Some physicians have candidly expressed real apprehension at the thought of possible litigation for malpractice if death or complications were to develop in some of their patients not receiving these drugs.

In order to justify the use of anticoagulants in all patients with acute myocardial infarction, it must be proved that even in seemingly benign instances of the disease the preventable mortality and morbidity significantly exceeds the incidence of complications and death attributable to the drug itself. Obviously, if the benefit to be derived from dicumarol in selected patients is found to be negligible when weighed against the hazards of hemorrhage inherent in this form of treatment, the needless expenditure of "time, trouble, and money" required to carry out this therapy would indeed be a wasteful extravagance. It is important, therefore, to determine whether the anticoagulant, like any other drug, may be indicated only under certain well defined circumstances. Anticoagulant therapy requires hospitalization for many patients who could otherwise be treated satisfactorily at home. It increases the cost of medical care by the added expense of laboratory tests and by the necessity for more frequent visits by the Attending Physician. It has contributed to the overcrowding in our hospitals and to the increased pressure upon the laboratory facilities of these institutions. There is good reason to believe that it may be well worth its price in the more serious cases of acute myocardial infarction, but whether

or not this can also be claimed for the milder cases of the disease has become a subject of editorial comment,[22, 23] investigation[24–26] and debate.[27, 28]

In previous studies,[24, 25] we have found that there is a strikingly low mortality rate and incidence of thromboembolism in selected "good risk" cases of acute myocardial infarction which are treated by conservative methods, exclusive of anticoagulant drugs. In order to study the natural course of the disease in such cases without specific treatment, we eliminated those which showed one or more of the following serious prognostic signs: (1) previous myocardial infarction; (2) intractable pain; (3) extreme degree or persistence of shock; (4) significant enlargement of the heart; (5) gallop rhythm; (6) congestive heart failure; (7) auricular fibrillation or flutter, ventricular tachycardia or intraventricular block; (8) diabetic acidosis, marked obesity, previous pulmonary embolism, varicosities in the lower extremities, thrombophlebitis (past or present) or other states predisposing thrombosis. The patients who showed none of these criteria on the first day of hospitalization were classified as "good risks" to distinguish them from the "poor risk" group comprising those who manifested one or more of these unfavorable prognostic signs. The material was derived from the Maimonides and Kings County Hospitals in Brooklyn and the United States Public Health Service Hospital in Staten Island. An analysis was made of 1,047 consecutive admissions for acute myocardial infarction of which 223 were treated at the Maimonides Hospital, 623 at the Kings County Hospital, and 201 at the United States Public Health Service Hospital. Approximately 60 per cent of the total group were admitted on the day of their attack. In every instance, the clinical diagnosis of acute myocardial infarction was confirmed by one or more electrocardiograms. The age range for the entire series was 30 to 88 years. There were 843 men and 204 women. All of the patients were treated by conservative means without the use of anticoagulants. In the classification of patients into "good risk" and "poor risk" groups, only the facts in the history and physical examination which were available on the first day of admission to the hospital were considered. After such classification was complete, a study was made of the clinical course and subsequent outcome in each case. Our analysis showed that the mortality rate for the 1,047 cases in our series during the period of hospitalization was 33.4 per cent. When the patients were classified according to the clinical findings on the day of admission to the hospital, however, it was found that the mortality rate in the "good risk" group was only 3.1 per cent as compared to 60.0 per cent in the "poor risk" group. Similarly, the incidence of thromboembolic complications was 6.0 per cent in the total group, 10.6 per cent in the "poor risk" group and only .8 per cent in the "good risk" group (Table I).

TABLE I

Mortality Rate and Incidence of Thromboembolic Complications

| | | Mortality | | Embolization | |
|---|---|---|---|---|---|
| | *No. Cases* | *No.* | *Percentage* | *No.* | *Percentage* |
| Total | 1047 | 350 | 33.4 | 63 | 6.0 |
| "Good Risk" | 489 | 15 | 3.1 | 4 | 0.8 |
| "Poor Risk" | 558 | 335 | 60.0 | 59 | 10.6 |

These results show that in the clinical material provided by the patients who gain admission to our hospitals, there is a strikingly low mortality rate and incidence of thromboembolism among those who qualify as "good risks" when first seen on the day of entrance. With a mortality rate of only 3.1 per cent and an incidence of thromboembolism of .8 per cent, one appears justified in questioning the possible benefit which could be derived from the use of dicumarol in such selected cases. In attempting to determine the possible theoretical benefit which might have been achieved with the use of this drug in our 489 "good risk" patients, an analysis was undertaken of the causes of death in this group (Table II). Of the 15 fatalities in the 489 "good risk" cases, seven occurred within 48 hours

TABLE II

Analysis of Causes of Death Among "Good Risk" Patients

*15 Fatalities in 489 Cases*

| | |
|---|---|
| Within 48 Hours | 7 |
| Unrelated Causes | 2 |
| Rupture Left Ventricle | 1 |
| Cerebral Embolus | 1 |
| Unknown | 4 |
| | 15 |

of admission to the hospital, and it is therefore unlikely that these could have been prevented by dicumarol. Two patients died from causes unrelated to their cardiovascular disease (one from peptic ulcer and one from septicemia and bronchopneumonia). One patient died from rupture of the left ventricle and at autopsy there was no evidence that thromboembolism played any part in this termination. These ten deaths, therefore, could not have been prevented by dicumarol. One patient died from a cerebral embolus and the remaining four patients died from causes not definitely known since autopsy was not obtained. If it is assumed that the latter five deaths could have been prevented under dicumarol therapy (an assumption lacking confirmatory evidence), the theoretically preventable mortality in our "good risk" group would have been five out of 489 or 1.0 per cent. Consequently, no more than one death among every hundred patients in our series who sustained a mild attack could have been prevented if the prophylactic effect of dicumarol was infallible. Moreover, if the drug worked to perfection (and this is certainly far from the truth), it could avert only eight clinical thromboembolic episodes in every 1,000 patients since this was the total incidence of the complication in our "good risk" group. Even if minor episodes had been overlooked, such small theoretical benefit is certainly unimpressive when balanced against the risks inherent in any interference with blood clotting.

Increasing numbers of case reports are appearing in the literature in which hemorrhagic complications and death have resulted from the use of anticoagulants. Sporadic reports of single cases or groups of cases give no assistance in determining the relative frequency of deaths due to dicumarol, but they do indicate that such results can be encountered by physicians experienced in anticoagulant therapy. As stated in a recent editorial,[29] "the incidence of hemorrhage following the use of anticoagulants depends to some extent on the philosophy of the clinician who may be inclined to push the dosage in the belief that

it is more desirable to assure patients with cardiovascular disease full protection against thromboembolic complications, thus running some risk of hemorrhage rather than to use a dose carrying with it so little chance of hemorrhage that it might fail to inhibit intravascular clotting." The data collected by Nichol,[20] summarizing the experience of 136 physicians, showed that major bleeding occurred in 2 per cent of approximately 15,500 anticoagulant-treated patients. The chief site of major hemorrhage was reported to be the urinary tract. In Nichol's own experience, the incidence of major hemorrhage was 10 per cent. The mortality rate in his collected group of 15,500 patients from hemorrhage induced by heparin or dicumarol was .18 per cent. Most of the available statistics concerned with the dangers of anticoagulant therapy, however, reflect the experience of skilled investigators in large medical centers where excellent facilities for prothrombin determination exist. Consideration should be given to the probable results of therapy administered in smaller hospitals or in the patient's home under the guidance of less skilled hands. It must not be overlooked that general practitioners and not "scientific investigators picked for their outstanding reputation in heart disease" treat the vast majority of patients with acute myocardial infarction. Moreover, it is in the milder cases that the general practitioner is likely to have exclusive control without benefit of consultation.

Wright and his associates[16, 18, 19] observed no improvement in death rate in unselected dicumarolized patients under 60. Obviously, if this therapy does not influence the death rate in groups in which thromboembolism is said to be prevalent, it should not be expected to serve any useful purpose and, in fact, may be detrimental in selected "good risk" cases in which, as we have shown, the incidence of thromboembolism is strikingly low. The observation that dicumarol improved the mortality rate only in older patients warrants careful analysis. Wright's interpretation of this finding is that younger people survive thromboembolic complications more readily than older people even though they have as many or more. This explanation, however, appears untenable since other workers have found that the improvement of prognosis by anticoagulant therapy is independent of age. The failure to demonstrate a reduction in mortality among dicumarolized patients under 60 could be more logically explained by the fact that relatively few of the patients in the series of Wright and co-workers were admitted to the hospital on the day of their attack, so that the institution of therapy was unavoidably delayed in most instances. Moreover, the low mortality rate of 10 per cent, which was reported for the control group under the age of 60, would seem to suggest that the control sample at least contained relatively few instances of serious attacks. For a similar group of patients, Tulloch and Gilchrist[20] reported a mortality rate of 29.0 per cent and our own studies[22] showed the frequency of death to be almost identical (28.8 per cent). Consequently, either the control series of Wright and associates may not have been comparable to their treated series in the younger age group or, if it was, the relative paucity of serious cases may not have permitted anticoagulants to be statistically life-saving.

Our findings[23] are not in accord with the view which assumes that age *per se* is a determinant of the individual patient's ability to survive an acute attack of myocardial infarction. It is true that crude statistics show that the mortality rate from this disease increases with advancing years but such statistical differences could be due simply to a higher incidence of severe attacks in later life rather than to a specific influence of age on

survival in the individual case. No evidence has been produced to date to justify the common belief that a patient over the age of 60 has a greater chance of dying from acute myocardial infarction than a younger patient who has sustained an attack of similar severity. Previous mortality studies have not been corrected for differences in the severity of attacks, the clinical signs or the incidence of previous myocardial damage. Obviously, similar cases must be compared in different age groups if a true concept is to be formulated regarding the elderly patient's relative capacity for survival. Our studies actually demonstrate that the elderly "good risk" patient or "poor risk" patient has no worse a chance for survival than the younger patient with similar clinical findings. It can be seen from Table III that less than half of the patients under the age of 60 were "poor risk" cases,

TABLE III

Analysis of 1047 Cases of Acute Myocardial Infarction
According to Age and Severity of Attack

| | *Total* | *"Good Risk"* | *"Poor Risk"* |
|---|---|---|---|
| All Ages | 1047 | 489 (46.7%) | 558 (53.3%) |
| Under 60 yrs. | 618 | 331 (53.6%) | 287 (46.4%) |
| 60 yrs. or over | 429 | 158 (36.8%) | 271 (63.2%) |

whereas almost two-thirds of those 60 years of age or older belonged to the same category.

When the mortality rates were calculated on the basis of age and the severity of the attack, it was found that age had no influence on prognosis (Table IV). The "good risk"

TABLE IV

Mortality Rate in 1047 Cases of Acute Myocardial Infarction
According to Age and Severity of Attack

| | *Total* | *"Good Risk"* | *"Poor Risk"* |
|---|---|---|---|
| All Ages | 33.4% | 3.1% | 60.0% |
| Under 60 | 28.8% | 3.0% | 58.5% |
| 60 or over | 40.1% | 3.2% | 61.6% |

patients of either age group had a strikingly similar death rate (3.0 per cent as compared with 3.2 per cent). Similar findings were noted from comparison of the "poor risk" groups (58.5 per cent as compared with 61.6 per cent). It can be seen that this important information had heretofore been buried in the overall statistics reflecting age group prognosis. The higher mortality rate recorded for old age groups is therefore merely a statistical phenomenon of interest to the actuary, but of little real significance to the practicing physician. Our observations seem to indicate that the history and the clinical signs and symptoms in any given case, and not the age of the patient, provide the data necessary for prognostication and for decision with regard to the use of anticoagulant drugs. Any increased benefit recorded from anticoagulant therapy in older age groups would therefore appear to depend on the much higher incidence of serious attacks in older people and the correspondingly higher incidence of thromboembolism. The "good risk" elderly patient is no more in need of anticoagulants than the "good risk" younger patient. Moreover, the risk from hemor-

rhage is probably greater in older groups because of the greater prevalence of unrecognized contraindications to therapy. It would seem, therefore, that the small benefit to be derived from dicumarol in "good risk" patients of any age is more than likely to be nullified or even overbalanced by complications induced by this drug. In our opinion, it should be reserved for the more serious cases of acute myocardial infarction in which the frequency of thromboembolism justifies the risk entailed in its use.

The search will continue for an effective anticoagulant that combines safety with simplicity of administration and control. If such a drug can be found, then most of the objections to anticoagulant therapy will be dispelled. There have been a number of newer anticoagulant drugs of which the ethyl ester of 4-hydroxycoumarin or Tromexan is the most commonly employed. Chemically it is very similar to dicumarol. It is approximately 1/5 as potent as the latter, milligram for milligram, and, therefore, the dosage is approximately five times as great. The only differences between the action of Tromexan and dicumarol is that the effect of Tromexan develops somewhat more rapidly after administration has been started and disappears somewhat more rapidly after administration has been discontinued. Individual differences in sensitivity to Tromexan are similar to those noted with dicumarol, and when the drug is given, it is equally necessary to establish the correct dosage on the basis of daily determinations of prothrombin time. An original dose of 1,200 to 1,500 milligrams is recommended, and the usual daily dose for maintaining prothrombin deficiency in the therapeutic range is considered to be 600 to 900 milligrams. It is believed by some that there is a greater safety factor in using Tromexan than in using dicumarol because of the more rapid subsidence of effect after administration of the drug has been discontinued. For this reason there has been a swing from dicumarol to Tromexan in some centers. However, the prothrombin time of some individuals does not return to normal for as long as four or five days after the last dose of the drug is given. As Barker[31] has stated, the only disadvantage of Tromexan over dicumarol appears to be a somewhat greater difficulty in maintaining the prothrombin deficiency within the therapeutic range during the trial period or first week or two of administration because of the tendency to more rapid fluctuations of the prothrombin time. Splitting the daily dose appears to reduce these fluctuations. To date, an insufficient number of patients have been treated to determine whether the drug is as effective as dicumarol in preventing thrombosis and whether the risk of bleeding is less than when dicumarol is used.

At the present time, experiments are being carried out in certain centers on small groups of patients in whom dicumarol therapy has been continued indefinitely following an attack of acute myocardial infarction in the hope of preventing recurrent attacks. One of the most interesting reports is that of Nichol and Borg[32] who recently reported that since 1944 such therapy has been administered continuously in 78 patients. Twelve of these patients have died, but only four of the latter had recurrent coronary thromboses. Autopsy studies were obtained in eight of the twelve deceased. Nine patients discontinued therapy. Fifty-seven patients remaining on the regimen were active and doing well with little anginal complaint, and, in ten of these, two or three years had passed without an attack. In one noteworthy case in which three previous myocardial infarctions had occurred, five years had passed since the past recurrence. Four of the living patients had experienced episodes of acute coronary insufficiency with possible subendocardial infarction followed by re

covery without thromboembolic complications. Only one patient, who was elderly, developed a recurrent myocardial infarction while dicumarolized. Major hemorrhagic episodes occurred in 13 patients resulting in two fatalities, only one of which could fairly be attributed to the use of dicumarol. Hemorrhage necessitated abandonment of the regimen in three other patients; the remainder resumed dicumarol treatment satisfactorily. No toxic effect on the kidney or liver was found in seven autopsy subjects who had received dicumarol for two to twenty-three months, nor had clinical evidence of such toxicity been found in the living patient. It is obvious that no conclusions can be drawn from such studies of small groups of patients because of the difficulty of obtaining comparable controls.

There can be little doubt that anticoagulant therapy in acute myocardial infarction is here to stay. Whether or not it should be used routinely for all cases of this disease is quite another matter. Our own opinion is that with the drugs now available, this therapy should be reserved for the more serious cases of acute myocardial infarction in which the frequency of thromboembolism justifies the risk entailed in its use. In the milder cases, the employment of such measures as the low bed, bedside commode, early armchair treatment, and mild active and passive exercise to encourage circulation in the extremities would leave little room for even theoretical benefit from the use of anticoagulant drugs. Even in the more severe cases such physical measures are more than likely to diminish the benefits to be expected from this form of therapy.

In order to determine the current opinions of leading internists and cardiologists concerning the use of anticoagulant drugs in acute myocardial infarction, a questionnaire was forwarded to a large number of such specialists in various medical centers throughout the United States. On the basis of 228 replies received in this manner, a crosssection of authoritative opinion was obtained which may be summarized as follows:

(1) More than half (50.9 per cent) of the 228 physicians interrogated in this survey do not employ anticoagulants as a routine measure in the treatment of acute myocardial infarction. Even when no contraindications exist, 111 of these specialists are guided entirely by the history and the severity of the clinical signs and symptoms in the individual case. Five physicians do not use anticoagulant therapy at all since they strongly doubt that its value outweighs its potential hazards.

(2) The 111 physicians advocating selection of cases on the basis of clinical findings enumerated the following criteria as indications for anticoagulant therapy: previous myocardial infarction, the presence of a large infarct, profound or persistent shock, intractable pain, significant enlargement of the heart, cardiac arrhythmias, thromboembolic phenomena, varicosities, previous or recent thrombophlebitis or phlebothrombosis, old age, debility, lethargy, obesity, diabetes, polycythemia and any other departure from a smooth or uneventful course.

(3) Most physicians in the former group regard old age as an important indication for the use of anticoagulants, but several of them consider it to be a distinct contraindication. The fallacy regarding age as a significant factor in prognosis in the individual case has already been emphasized by the authors.

(4) There were 112 or 49.1 per cent of the 228 physicians in the total series who reported that they routinely employ anticoagulants in all cases of acute myocardial infarction when

no contraindications exist. A small number of this group emphasized that they have actually been forced to follow this practice since failure to use these drugs "is often construed by the family, referring physician and consultant, as mistreatment."

(5) There was unanimity of opinion regarding the necessity for hospitalization and dependable laboratory facilities in every case of acute myocardial infarction in which anticoagulants are to be employed.

(6) Among nonmedical factors influencing the decision to employ or withhold anticoagulant drugs were: a) economic status of the patient; b) coercion by the patient's family or referring physician; c) the compelling influence of the wide publicity given to this form of treatment; d) fear of criticism or litigation for malpractice if such treatment were withheld.

(7) Most physicians who replied to the questionnaire either used dicumarol alone or in combination with Heparin. More than half of those who employ Heparin reserve it exclusively for the more serious cases. Only 31.6 per cent of the total of 228 physicians invariably prescribe this drug when ordering dicumarol. Tromexan is being used alone or in conjunction with dicumarol and/or Heparin by a smaller but significant number of the physicians contacted in this study.

(8) Serious hemorrhagic complications resulting from anticoagulant therapy were encountered by 104 or 45.6 per cent of the 228 physicians in this study. One hundred twenty-two deaths caused by such complications were reported by 64 or 23.7 per cent of the total group. The brain, gastrointestinal tract, and pericardium in this order were found to be the commonest sites of fatal hemorrhage. Individual reports of the incidence of major hemorrhage based on personal observations varied from 0.25 per cent with no deaths from this complication, to 10.0 per cent with four fatalities due to hemorrhage in 100 anticoagulant-treated patients.

From the foregoing, it is concluded that neither the evidence to date nor the current method of usage by authorities in the field can support the concept that the routine employment of anticoagulant therapy in acute myocardial infarction is necessary or desirable.

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# ABSTRACTS

## infectious diseases

1. *Stevens-Johnson Syndrome Occurring in Identical Twins with Apparent Response to Terramycin and Aureomycin.* J. H. PRITCHETT JR. AND A. C. AUSTIN, Bremen, Georgia. J. M. A. Georgia *40*:374–6, September 1951.

Two cases of Stevens-Johnson syndrome are reported. Penicillin and streptomycin cleared the complicating pneumonitis of the first case without altering the florid development of the collagen syndrome. Improvement, which could have been the natural course of events without the administration of terramycin and aureomycin, began with the oral administration of these antibiotics.

Oral administration of terramycin and aureomycin to the second of the twins did not prevent the development of the cutaneous eruption, conjunctivitis, or vesicular stomatitis, but did appear to decrease definitely the length and severity of the illness as compared to that of the first patient.—*Author's abstract.*

2. *Bacteremia Due to Gram-negative Bacilli Other than the Salmonella: A Clinical and Therapeutic Study.* BURTON A. WAISBREN, Milwaukee, Wis. A. M. A. Arch. Int. Med. *88*:467–88, October 1951.

Twenty-nine cases of bacteremia due to gram-negative bacilli other than the *Salmonella* were presented. The most common portal of entry was the genitourinary tract, and the most common precipitating factors, catheterization and instrumentation. Two distinct clinical pictures were seen. In one the patient appeared toxic and in the other shocklike. The patients suffering from bacteremia due to *Proteus* appeared to be the most severely ill. The majority of patients exhibited a marked febrile and leukocytic response. A therapeutic approach to patients in whom bacteremia due to gram-negative bacilli is suspected was presented. Emphasis was placed on nonspecific as well as specific therapy. Examples were given of the use of the laboratory in the management of these patients. The possible roles of antimicrobial therapy in indirectly causing certain types of infection and in bacterial evolution were discussed. 19 references. 5 tables.—*Author's abstract.*

3. *Enhanced Activity of the Basic Antibiotics.* CHARLES H. MANN, Princeton, N. J. Antibiotics and Chemotherapy *1*:242–44, July 1951.

Newer developments in the formulation of combination antibiotics and chemotherapeutic agents now provide more pronounced therapeutic effectiveness against diseases caused by mixtures of micro-organisms. Although penicillin and strepto-

mycin are well established in clinical practice, it is increasingly evident that these basic antibiotics, when administered individually, are limited in their effectiveness against mixed infections. In consideration of this problem, efforts have been made to provide enhancement or synergistic activity by employing combinations of two or more antibiotics or chemotherapeutic agents to obtain full therapeutic effect against a greater number of pathogenic organisms.

The theory of the mechanism of enhancement or synergistic activity of antibiotics and chemotherapeutic compounds is presented.

The development and clinical usage of first, the combination of sulfonamides, and second, the combination of the sulfonamides and antibiotics, and more recently, the combination of various antibiotics, is described with proper attention given to the types of sulfonamides and antibiotics currently being used in medical practice.

Combination antibiotic therapy is rapidly becoming valuable in the therapeutic armamentarium of the medical profession and micro-organisms heretofore responsible for the majority of human infections are rapidly being brought under efficient control. 3 references.—*Author's abstract.*

1. *Laboratory and Clinical Studies on Terramycin.* ELLARD M. YOW, DANIEL E. JENKINS, HENRY E. MENDELL, RAY H. SKAGGS, AND HAROLD R. HIPP, Houston, Texas. Am. Pract. 2:689–93, August 1951.

This paper deals with clinical and laboratory observations made on 60 patients with varied infections that were treated with terramycin. In each case *in vitro* sensitivity tests were performed parallel with the clinical trail. The *in vitro* sensitivity tests revealed that most of the organisms tested were quite sensitive to terramycin except that none of the strains of *Proleus* were sensitive, most of the strains of *Pseudomonas* were resistant and an occasional strain of staphylococcus was resistant. The clinical response was quite closely correlated to the sensitivity of the causative organism in cases where other factors such as adequate urinary drainage were controlled. Terramycin was found to be beneficial in both lobar and mixed bacterial forms of pneumonia, acute pharyngitis, urinary tract infections due to susceptible organisms, intestinal amebiasis, granuloma inguinale, lymphogranuloma venereum, and in one case each of brucellosis due to *Brucella suis*, shigella dysentery, and tularemia. It was of no value in infections due to *Bacillus proleus* and of value in *Pseudomonas* infections only when the organism was sensitive to the antibiotic. No beneficial effect was seen in a case of Hodgkin's disease, sarcoidosis and tuberculous meningitis. No serious untoward reactions were noted, but patients occasionally complained of nausea, vomiting, and diarrhea. Epigastric distress was noted in 3 of the 60 patients, nausea in 8, vomiting in 7, and diarrhea in 5. No allergic reactions were seen and in 41 of the patients no untoward reactions of any type were noted. When leukocytosis was present prior to institution of terramycin therapy, there was usually a prompt return of the white blood cell count to normal. A slight transient eosinophilia was frequently noted during the first two days of terramycin therapy. In this study the dose varied from 1.0 to 6.0 Gm. daily and was

usually a 100 mg. per Kg. per 24 hours. Smaller doses have been used with apparently equally good results. 22 references. 2 figures. 4 tables.—*Author's abstract.*

5. *Penicillin Therapy of Typhoid Fever.* NELSON H. SCHIMMEL, WALTER V. MATTEUCCI AND WILLIAM P. BOGER, Philadelphia, Pa. J. M. Soc. New Jersey *48*:323–25, July 1951.

The relatively high incidence of relapse in typhoid fever treated with chloramphenicol and the inability of this antibiotic to eliminate the carrier state make it desirable to continue the search for a more effective therapy for this disease.

Laboratory studies have shown the *in vitro* effectiveness of penicillin against S. typhosa. Previous attempts to apply this knowledge clinically have been unsuccessful. With our present knowledge of penicillin levels, these previous clinical failures are thought to be due to an inadequate penicillemia.

Three cases of typhoid fever were successfully treated with penicillin. Specific therapy consisted of 1,000,000 units of penicillin every three hours and Benemid 0.5 Gm. every six hours.

In the first case the fever curve showed a slow response, but the blood cultures were rapidly converted from positive to negative, and there was prompt reduction in the toxicity of the patient. Treatment in the second case was started late in the course of the disease and the response may have been the natural course of the disease; however, there was prompt reduction of toxicity. The third case was that of a chronic urinary carrier. The initial infection occurred in 1915, and he was thought to have been shedding organisms in the urine since that time. Urine cultures were converted to negative during treatment and remained negative for a two month follow-up period.

Blood level determinations showed that this dose of penicillin with the aid of Benemid was sufficient to maintain a lethal penicillemia in these patients at all times.

These cases support the hypothesis that penicillin in *adequate* doses is effective in treating typhoid fever.—*Author's abstract.*

6. *Tuberculous Meningitis: Correlation of Therapeutic Results with the Pathogenesis and Pathologic Changes. I. General Considerations and Pathogenesis.* OSCAR AUERBACH, Staten Island. Am. Rev. Tuberc. *64*:419–29, October 1951.

A study of tuberculous meningitis was made in an autopsy series of 2,333 patients who died of all forms of tuberculosis; 108 (4.6 per cent) had tuberculous meningitis, with 41 of these falling into the age group below, and 67 patients above, 12 years of age. The sex distribution was approximately parallel to that of the general autopsy series, but there was a noteworthy increase in the number of colored patients.

It was found that, whereas the childhood group invariably had primary pulmonary complexes, either in the progressive, liquifaction, or healing stages, the adult group was divided into those having chronic pulmonary tuberculosis, or chronic and acute miliary tubercules, or combinations thereof. In the adult group

only two cases failed to show pulmonary tuberculous lesions, other than healed primary foci. Since there was a close relationship between miliary spread and extrapulmonary, genital, or skeletal tuberculosis, it was felt that the former occurs secondary to the latter, and that the miliary spread in the lungs represents dissemination from the extrapulmonary foci.

The larger incidence of tuberculous meningitis in childhood (42.2 per cent), than in adults (2.9 per cent) was noted. The etiology of the former was related to the miliary spread from a primary pulmonary complex, whereas, in adults, it was considered that tuberculous meningitis arose primarily from miliary spread starting in an extrapulmonary focus. These are usually genital or skeletal, and progress through caseous regional lymph nodes into the blood stream. The only exception to this were tuberculous lesions in juxta-meningeal locations, which involved the meninges directly.

It was considered unusual that tuberculous meningitis arose secondary to chronic pulmonary tuberculosis *per se*.

Serial study of the brains of these cases have led to the conclusion that once the miliary spread has taken place, tuberculous caseous foci are established in the brain substance itself, or as meningeal plaques. The meningitic involvement is then a secondary dissemination from these foci. However, once these foci are encapsulated, they no longer take an active part in this process. 14 references. 7 figures.—*Author's abstract.*

7. *Aureomycin Treatment in a Newborn Premature Infant with Bacillus Coli-Meningitis.* G. LAURELL, J. H. MAGNUSSON, B. WERNER, Uppsala, Norway. Acta Paediatrica *40*:174–80, March 1951.

A report is given of a case of acute meningitis caused by coli bacilli in a newborn premature infant with scleredema. The coli strain was isolated. It proved to be very sensitive to aureomycin, and was also studied from the aspect of its serologic properties. The infant was treated with aureomycin with good clinical effect. 6 references. 2 tables.—*Author's abstract.*

8. *Comparative Efficacy of Several Antibiotics on Experimental Rickettsial Infections in Embryonated Eggs.* ELIZABETH B. JACKSON, Washington, D. C. Antibiotics and Chemotherapy *1*:231–41, July 1951.

The present work was undertaken to compare the efficacy of a number of rickettsiostatic agents under essentially identical conditions. The results enable one to arrange the drugs in a progressive series according to their activity in embryonated eggs. These data justify the statement that one substance has greater activity than another; however, such observations do not enable one to conclude that the substance which most effectively inhibits the growth of rickettsiae in eggs is the best therapeutic agent for treatment of patients.

The general order of rickettsiostatic activity of eight substances as judged on a gravimetric basis in embryonated eggs infected with one of a number of rickettsiae is as follows: terramycin, aureomycin, chloramphenicol, para-aminobenzoic acid,

nitroacridine, penicillin G, subtilin and streptomycin. This order does not hold in its entirety for all nine of the rickettsiae tested. However, terramycin, aureomycin and chloramphenicol are consistently the most active therapeutic agents while streptomycin is the least. Subtilin is more effective against *R. tsutsugamushi* than against *R. typhi* or *R. rickettsii* while the reverse order is true for para-aminobenzoic acid.—*Author's abstract.*

9. *Encephalitis in the Midwest: I. A Review of the Problem.* T. AIDAN COCKBURN, EDMUND R. PRICE, AND JOHN A. ROWE, Topeka, Kansas. J. Kansas M. Soc. 52:316–18, July 1951.

Two of the arthropod-borne virus encephalitides, western equine encephalomyelitis and St. Louis encephalitis, are endemic in the midwest, and have occurred in the past in epidemic form. Both humans and equines have been affected.

Large epidemics of encephalitis in horse and man have occurred in the states of the Missouri River Basin. Major epidemics of St. Louis encephalitis occurred in 1933 and 1937 in the city and county of St. Louis, Missouri, and of western equine encephalomyelitis in 1941 in North and South Dakota, Minnesota, and Nebraska. The equine epizootics (such as the "Kansas-Nebraska horse plague" in 1912 and those of 1937 and 1938, affecting the whole midwest) involved vast numbers of animals.

The Encephalitis Investigations Unit of the Office of Midwestern CDC Services is engaged in long-term investigations into the epidemiologies of these viruses in the hope of discovering some practical method of control. 20 references. 2 figures. —*Author's abstract.*

10. *Studies on the Clinical Pharmacology of Aureomycin.* HENRY D. BRAINERD, HENRY B. BRUYN, GORDON MEIKLEJOHN, AND LOUIS O'GARA, San Francisco, Calif. Antibiotics and Chemotherapy *1*:147–60, October 1951.

The absorption, distribution, and excretion of aureomycin were studied by means of determination of its concentration in various body fluids following administration of the drug in normal persons and patients suffering from various infectious diseases.

In determining the *in vitro* susceptibility to aureomycin of 162 strains of 18 species of common bacterial pathogens, it was observed that most gram-positive cocci were sensitive to less than 0.1 μg per milliliter; most gram-negative rods were sensitive to less than 1.7 μg per milliliter; and *Proteus vulgaris* and *Pseudomonas aeruginosa* were sensitive only to 3.5 or more μg per milliliter.

Following oral administration of 250 mg., aureomycin was detectable in the serum within one hour, reached a peak in two hours, and was still measurable in 4 of 7 subjects at twelve hours, but not at twenty-four hours. Following the ingestion of 1 Gm. by mouth, peak concentrations were noted at four hours, were still high at twelve hours, and aureomycin was still detectable in the serum of three of seven subjects twenty-four hours after administration. By determining the areas under the curves representing average serum levels at various periods after admin-

istration, it was found that the total amount of aureomycin absorbed during the first six hours after the oral administration of 250 mg. was not significantly less than that following the oral ingestion of 1 Gm. On the other hand, the total amount of aureomycin absorbed in 24 hours was much greater for the larger dose. This suggested that aureomycin was absorbed from the gastrointestinal tract at a maximal rate which could not be increased by increasing the dose fourfold.

Following intravenous administration of aureomycin, immediate peak serum concentrations were observed which declined gradually. In three of four subjects who received 500 mg. intravenously, measurable serum concentrations were present twenty-four hours later. By determining that the total amount of aureomycin present in the body over a six-hour period was three times as great following the intravenous injection of 100 mg. as compared to 50 mg., instead of the expected twice-as-great it appeared that aureomycin could be excreted at a maximum rate by the kidney which could not be increased by increasing the amount administered.

Aureomycin was poorly absorbed after intramuscular injection, producing only low or inconsistent serum concentration. If 250 viscosity units of hyaluronidase were added to the aureomycin, absorption was increased several-fold after intramuscular injection.

Aureomycin was rarely demonstrated in the serum following rectal administration, but absorption was demonstrated in one patient following aerosolization.

Measurable concentrations of aureomycin in the cerebrospinal fluid were noted in only two of eleven determinations in patients receiving the drug both by the oral and intravenous routes. Diffusion of aureomycin into pleural fluid was noted in three of nine determinations and occurred only in patients who had been receiving large amounts of aureomycin for periods of 24 or more hours. The drug appeared to diffuse readily into inflammatory joint fluid. Aureomycin was noted in the bile of one or two persons who received the drug by mouth. The gastric juice of one person contained no aureomycin two hours after the intravenous administration of 200 mg. High concentrations were found in the stools, however, of patients receiving the drug by mouth and presumably represented incomplete absorption.

While aureomycin appeared in high concentration in the urine of individuals receiving aureomycin, accurate measurement was impossible because of deterioration of aureomycin in urine specimens when it existed in concentrations of less than 100 $\mu$g. per milliliter, especially at *p*H in excess of 7.0. In addition, considerable loss of aureomycin was noted ducing Seitz filtration of urine specimens.

Most patients receiving 4 or more Gm. of aureomycin a day experienced nausea, epigastric distress, or anorexia, and frequently vomiting. Occult blood was demonstrated in the stools of several persons receiving large amounts of the drug by mouth. Nausea was minimal after intravenous injection or following the ingestion of doses of 250 mg. every six hours. Diarrhea was common at both dosage levels. Skin rashes occurred in 6 of 116 patients treated with aureomycin. In addition, glossitis and perineal erythema and pruritus were noted. Two instances of rashes occurring after exposure to sunlight were observed. 6 figures, 3 tables.—*Author's abstract.*

11. *Aureomycin and other Antibiotics in the Treatment of Acute and Chronic Amebiasis.* H. L. LEY, W. S. SAYER, A. C. S. HOBSON, R. M. VANREENEN, V. J. TIPTON, L. P. FRICK, E. L. BALLARD, AND R. TRAUB, Washington, D. C. Antibiotics and Chemotherapy *1*:281–88, August 1951.

Treatment of 12 persons in Malaya with acute intestinal amebiasis with 2.0 Gm. aureomycin daily for 13 or 14 days resulted in prompt control of clinical manifestations and disappearance of *Endamoeba histolytica* from the feces. However, permanent elimination of the parasite was only accomplished in 5 of 8 persons in whom follow-up examinations were possible.

Chronic intestinal amebiasis was eliminated in 14 of 16 American patients treated with 21 to 29 Gm. aureomycin over a period of 10 to 14 days. Cysts of *E. histolytica* were found in the feces of one patient within 2 weeks after the end of therapy, and within 6 months in another patient.

Chloramphenicol appeared to be of no value in the treatment of 4 patients with chronic amebiasis.—*Author's abstract.*

12. *Study on Etiology, Epidemiology and Antibiotic Therapy of Infantile Diarrhea with Particular Reference to Certain Serotypes of Escherichia Coli.* ERWIN NETER, CHARLES R. WEBB, CLARE N. SHUMWAY AND MIRIAM R. MURDOCK, Buffalo, N. Y. Am. J. Pub. Health *41*:1490–96, December 1951.

This report summarizes the authors' observations on the etiology, epidemiology and antibiotic treatment of infantile diarrhea associated with the presence of certain serotypes of *E. coli*. It is noted that, in a review on epidemic diarrhea in the newborn by Gordon and Rubenstein, in 1950, the possible relationship of these types of *E. coli* to this malady is not even mentioned.

Two serotypes of *E. coli* (0111 and 055) were demonstrated in the feces, nasopharynx and throat of sporadic cases of infantile diarrhea. It is shown that contact with and multiplication of these types of *E. coli* may result in an attack of diarrhea, suggesting that these organisms may be the cause of this disease. Infants may be carriers of these organisms and have no history or evidence of diarrheal disease. In 11 out of 14 cases, the organisms were recovered from the upper respiratory tract, suggesting spread to other susceptible infants by airborne infection. *In vitro*, all strains of these serotypes of *E. coli* were susceptible to the broad spectrum antibiotics, chloromycetin, aureomycin, and terramycin and distinctly less so to streptomycin. They were essentially resistant to penicillin and bacitracin. The clinical administration of aureomycin, chloromycetin, and terramycin partially suppressed or eliminated these organisms from the intestinal and upper respiratory tract, with concomitant clinical improvement. Thus far, the authors have treated 9 cases of diarrheal disease associated with the presence of these organisms with aureomycin, terramycin, or chloromycetin. Five patients were given aureomycin by mouth in doses of 50 to 70 mg. per Kg. per 24 hours, with resulting disappearance of the organism within 4 days. The same results were noted in 2 patients receiving terramycin in doses of 65 to 70 mg. per Kg. every 24 hours. Chloromycetin given in intramuscular doses 35 mg. per Kg. per 24 hours resulted in disappearance of

large numbers of the organisms from the throat and feces within 3 days. The organisms present in the throat and nasopharynx of another patient were suppressed but not eradicated following injections of injectable chloromycetin in doses of 150 mg. per Kg. every 24 hours for 7 days. Intramuscular injections of chloromycetin in a preparation which may be administered intramuscularly or intravenously has yielded promising results for cases in which this drug is indicated, but cannot be administered orally. 22 references. 2 tables.

13. *Recent Developments in the Prophylaxis of Rabies.* HILARY KOPROWSKI AND HERALD R. COX, Lederle Laboratories, Pearl River, N. Y. Am. J. Pub. Health *41*:1483–89, December 1951.

It has been established that the Pasteur treatment for the prophylaxis of rabies in persons bitten by possibly rabid animals has only questionable value in cases where the wound inflicted is severe and that the treatment is occasionally followed by neuroparalytic accidents. The physician must, therefore, balance the risk of the vaccination procedure with the possibility that the patient may contract rabies. The WHO outline for antirabic treatment is presented in tabular form and the contraindications to antirabic treatment as enumerated by Sellers are listed. In 1948 concentrates of antirabic serum were made available in this country and each phial was accompanied by a questionnaire, which the physician responsible for the case was asked to fill out and return to the Lederle Laboratories. The results showed that a total of 48 cases received the antiserum, and of these, 11 were exposed to the bites of nonrabid animals. Eight persons were bitten by animals not captured and the bite was severe in 4 cases and moderate in 4 cases. The largest group in the series comprised 29 persons treated with the antiserum after having been bitten by animals proved to be rabid. Of these, 8 were bitten on the head or neck, 19 on the arms or hands, and 2 on the legs or feet. Nine showed severe exposures, 12 moderate and 8 mild. In most of these cases, administration of the serum was followed by phenolized vaccine treatment of varying duration and intensity. There were no fatalities. Since it is impossible to define actual exposure, a statistical evaluation of the effect of antiserum would prove difficult, but experimental evidence is strong in its favor and no person who has received the antiserum has as yet died of rabies. In every case of severe exposure, the use of antiserum should be considered, as soon after exposure as possible, within 24 hours if possible, and not later than 72 hours. At present it may be advisable to use antiserum treatment in conjunction with vaccine, to shorten the course of vaccine and thus diminish the risk of neuroparalytic accidents. The vaccine can be administered 24 hours after giving the antiserum, but can presumably be given at any time within 7 to 10 days. The psychologic effect of antiserum has also to be considered, and for this effect a dose of 0.50 ml. per Kg. of body weight is recommended. Serum sickness occurred in 20 per cent of those receiving rabbit serum concentrates and in many more of those receiving sheep serum concentrates. The production of the latter has therefore been discontinued. Should future experience confirm experimental findings, it may prove feasible in the future to further

reduce the number of injections of phenolized vaccine following antiserum treatment. When clinical trials confirm the safety and effectiveness of the chick-embryo-adapted Flury strain of rabies virus, this strain may be considered for human use. 19 references. 2 tables.

14. *Preliminary Report of Histoplasmin and Other Antigen Sensitivity in North Carolina.* ROBERT J. MURPHY, WILLIAM M. PECK AND BLANCHE VINCENT, Raleigh, N. C. Am. J. Pub. Health *41*:1521–25, December 1951.

Recently mass x-ray surveys in North Carolina have shown sectional differences in the incidence of multiple calcifications due to histoplasmin sensitivity. In the state as a whole the incidence of this type of sensitivity has been considered as low, but in certain areas it is apparently much higher. Skin tests with histoplasmin antigen were made in the patients in the three state tuberculosis sanatoria, in a group of persons having calcifications and in an unselected group from a county having a high incidence of pulmonary calcifications. The source of the testing material and the technic of the tests are described in detail. Five per cent of 925 sanatorium patients from 97 counties showed a positive reaction to histoplasmin. The regional incidence of sensitivity varied from 0.9 per cent in the north central section to 15 per cent in the northeastern section.

In the counties in the northeastern section, Beaufort county investigations revealed that 75 per cent of 147 patients with pulmonary calcification reacted to histoplasmin. In Hyde county, 43 per cent of 338 persons selected at random reacted to histoplasmin. The pulmonary calcification observed in the persons showing a positive reaction to histoplasmin in Beaufort county was similar to that described by others and related to histoplasmin sensitivity. Further investigations and skin tests for histoplasmosis in North Carolina are planned. 6 references. 3 figures.

# oncology

15. *Bronchogenic Carcinoma. A Report Comparing Three Consecutive Series of One Hundred Cases Each.* WILLIAM E. BLOOMER AND GUSTAF E. LINDSKOG, New Haven, Conn. Cancer *4*:1171–75, November 1951.

The present report concerns the third consecutive series of 100 cases of bronchogenic carcinoma admitted to the New Haven Hospital from May, 1947 to April, 1949. Most of the findings were similar to those reported in the first series (1938–1943) and second series (1943–1946). The average duration of symptoms prior to admission was longer in the second series (9.1 mo. as compared to 6.7 mo.), but this was attributed to increased difficulty in obtaining early medical care during the rush and shortages of the war period.

The percentage of exploratory thoractomies was slightly increased in the second series (40 per cent as compared with 32 per cent). Resection showed a constant increase (21 as compared with 12 per cent), indicating a tendency toward in-

creased use of palliative and sometimes technically difficult resections rather than an increase in admissions with clearly and easily resectable lesions. A tabular comparison of the three series is presented.

Of the 100 cases in the third series, a positive tissue diagnosis was obtained during life in 91 cases, in one case only at postmortem. In 4 cases, the diagnosis was based on findings in the sputum or secretions obtained at bronchoscopy. Tissue diagnosis was first obtained by bronchoscopic biopsy in 40 cases, and at exploratory thoracotomy and resection in 17 cases. Biopsy of the peripheral lymph nodes afforded diagnostic information in 12 cases. Positive cytologic findings in the sputum or secretions obtained at bronchoscopy were obtained in 12 cases. Exploratory thoracotomy and biopsy was done in 6 cases. Other methods included needle biopsy in 4 cases (only in inoperable cases and preliminary to radiotherapy), biopsy from metastatic nodules in 3 cases, and examination of the pleural fluid sediment in one instance.

The average duration of symptoms before first admission was usually about 6½ months. The right lung was affected in 57 cases, the left lung in 42 cases, and both lungs in one case. The upper lobes were involved in 57 per cent of cases. It would appear that increased reliance should be placed on exploratory thoracotomy in early cases and that bronchoscopy is least effective in early cases suited for surgical treatment. The histologic types of carcinoma included 50 epidermoid carcinoma, 24 anaplastic carcinoma, and 17 adenocarcinoma.

Fifty-five cases were inoperable when first seen. Of 48 cases subjected to an exploratory operation, 31 cases, or 65 per cent, were resected, as compared with 37 per cent of those explored in the first series.

Long term cures were obtained only in resectable cases. In the first series, the five-year cure rate was 2 per cent, in the second series not more than 2 per cent, and in the third series has not yet been calculated, but will be less than 11 per cent.

The reason for these relatively poor results are to be sought in the relative paucity of early symptoms, the delay between onset of symptoms and report for treatment, and the invasive nature of many tumors even though discovered early.

There has been an encouraging increase in the percentage of tissue diagnoses during life and in the number of patients undergoing resection. There seems to be a greater tendency toward attempting palliative resection. 2 references. 5 tables.

16. *Testosterone Therapy of Metastatic Adenocarcinoma of the Thyroid with Remission. Case Report.* HENRY M. LEMON, IVER S. RAVIN, JOSEPH F. ROSS, JOHN H. SISSON, THOMAS J. ANGLEM AND A. W. BRANCA, Boston, Mass. Cancer 4:1176–91, November 1951.

A case of marked subjective and objective improvement in generalized adenocarcinoma of the thyroid maintained over a period of 9 months is described in detail as presenting the first demonstration of a successful application of steroid therapy in this type of cancer. Advancement in the therapy of this type of tumor is especially urgent, since external radiation provides palliation for radiosensitive

tumors only, and clinical remissions have been obtained with radio-active iodine treatment in less than 15 per cent of reported cases.

In a white woman of 53 years of age with osseous metastases from an adenocarcinoma of the thyroid, the administration of 100 mg. of testosterone propionate three times weekly brought about an almost complete remission which has lasted for 9 months. None of the metastases had shown any signs of significant accumulation of $I^{131}$, even when stimulated by thyrotropic hormone. The metastases were resistant to external radiation. A few weeks after beginning the testosterone therapy, pain and disabilities were relieved, and there occurred a rapid recalcification of both irradiated and nonirradiated lesions. After 3½ months of the hormone treatment, the patient developed nocturnal dyspnea which responded to aminophyllin suppositories. Some of the pelvic metastases failed to show radiologic evidence of response. The number of erythrocytes was above normal and the blood pressure mildly hypertensive. She complained of a mild intermittent choking sensation not related to exercise. The left lobe of the thyroid had slightly increased in size, but no evidence of disease. Four or five days after onset of treatment, there was a marked increase in appetite, relief of back pain, and improvement in the patient's mood. She gained in weight and after 3 months returned to her usual occupations as a housewife. Her back ached only when she became tired, and the lesions in the skull had healed completely. She was discharged on a moderately high calcium diet. Further trial of this hormone in the palliative treatment of thyroid carcinoma is urged. 17 references. 15 figures. 3 tables.

17. *Malignant Neoplastic Disease in the South African Bantu.* JOHN HIGGINSON, Johannesburg. Cancer *4*:1224–31, November 1951.

A study is presented of 500 consecutive histologically proven neoplasms observed in the Bantu general hospitals over a period of 2½ years. All types of tumor were seen, but no attempts to demonstrate the frequency of any particular type of tumor were made owing to the difference in age distribution of the contributing hospital population. The latter included patients of an age slightly younger than that accepted as having the highest incidence of cancer, and this fact might well explain earlier reports of a low cancer incidence in Bantu. Carcinoma of the liver occurred less frequently than in previous reports and carcinoma of the stomach was rare. The most frequently encountered type of cancer was cancer of the *cervix uteri*, tumors of the body of the uterus having a low incidence. The author suggests a scheme for obtaining an approximate estimate of cancer incidence in Bantu by studying the population of a particular native township and believes this method might also be of aid estimating cancer incidence in other primitive groups.

It is emphasized that in the people of Bantu, glandular tuberculosis may simulate carcinoma of the liver and tuberculous glioma of the brain may simulate glioma. Basal cell carcinoma was less common than the squamous type. Carcinoma of the esophagus seemed high as compared with carcinoma of the stomach.

which constituted 9.5 per cent of the gastrointestinal neoplasms. Peptic ulcer is uncommon in this region.

The incidence of carcinoma of the liver was high especially in the region of the Rand mines and hemochromatosis as an indication of deficient nourishment is common. There seems to be no evidence that carcinoma of the liver is of environmental origin or attributable to racial differences. 25 references. 6 tables.

18. *Psychological Mechanisms in Patients with Cancer.* HARLEY C. SHANDS, JACOB E. FINESINGER, STANLEY COBB AND RUTH D. ABRAMS, Boston, Mass. Cancer 4:1159–70, November 1951.

The authors have launched a pilot project in an attempt to understand the emotional reactions and to discover a method for modifying the severity of the distress and behavioral results in patients who have been informed that they are suffering from cancer. The emotional reactions vary individually and even in the same person, depending upon essential and accidental variables. The reaction will show the same general tendency, but the specific form and degree of reaction will vary according to heredity, environment, and circumstance. Such patients have to face the possibility of early death or a painful lingering survival. If the emotional reaction exceeds the limits of individual tolerance, distress results and the person will either attempt to conceal it or compensate for it.

The idea of having a cancer usually exerts a violently disruptive effect on the personality and changes the patient's whole future outlook. The information has the effect of a blow on the head, leaving the victim stunned and dazed. There ensues a resulting paralysis of initiative and further activity becomes purely mechanical. Some individuals have been known to become speechless. In some the emotional reaction is most intense. They say that they feel "unreal" (depersonalization). Others are seized with hysterical laughter or uncontrollable fear.

In many cases, the individual will try to attach the responsibility for his plight either on some wrongdoing of his own or attribute it to actions of others. Immediately the emotions of guilt and suspicion come into play with all dire consequences for the patient himself and those who surround him. Illustrative cases of these various types of reaction are described in detail. Only a few become resigned to the inevitable.

In attempting to manage and relieve these patients, physicians have underestimated the importance to the patient of his relation to his doctor. A supportive psychotherapeutic relationship with the physician presents the possibility of marked alleviation of the associated emotional distress. It is important, in this connection, that one physician should assume over-all responsibility for the whole course of his patient's illness, referring to other therapists for appropriate treatments, but remaining always in the background for consultation and discussion. Such a procedure is of course almost impossible in a crowded clinic or hospital, and the responsibility for this phase of treatment must usually be assumed by an experienced medical social worker.

To begin with, no suspicions should be mentioned to the patient until a histologic diagnosis has been made. Once he has been informed of his condition the physician may describe to him the type of treatment which will be recommended in many of several eventualities, and whether a greater or lesser operation will be required. In all cases, the patient should be given only as much information as he asks for. The physician must determine what his patient should be told. Another important item to be kept in mind is that the physician must make an attempt to keep his relationship with his patient at about the same intensity throughout the period of treatment.

The defense reaction displayed by the patient may pass through the whole spectrum of defense reactions as observed in psychoneurotic patients, with suppression, denial, depersonalization, dissociation, identification, regression and sublimination. Threats of suicide are not uncommon, although suicide in these patients is actually rare. As a matter of fact, those who contemplate such an extreme step usually improve following this cathartic expression of emotion. The more stoically inclined are not so well off. There have also been paranoid or depressive reactions or both. Once adaptation to the inevitable has been attained, the patient may enjoy peace of mind. 7 references.

19. *Effects of Intra-arterial Injection of Nitrogen Mustard.* J. R. BARBERIO, C. T. KLOPP, W. W. AYRES AND H. A. GROSS, Bethesda, Md. and Washington, D. C. Cancer 4:1341–63, November 1951.

A study is presented of intra-arterial injection of nitrogen mustard into animals by a modification of the Donovan method for intra-arterial injection of heparin. The tissues of the pelvis and pelvic organs will tolerate periodic injections of moderate doses of $HN_2$ into the abdominal aorta, and the tissue showing the greatest sensitivity is the rectal mucosa. An injection into human subjects was made through polyethylene tubing introduced through a branch of the femoral artery or external iliac artery and advanced in retrograde fashion until the tip of the tube was in the abdominal aorta.

The treatment was administered to 2 patients suffering from recurrent adenocarcinoma of rectal origin localized to the perineum. Resection of the rectum had been performed in both instances with an end colostomy so there could be no possibility of injuring normal rectal mucosa. The cases are reported in detail.

The survival time of dogs receiving nitrogen mustard injections through the arteries was inversely proportional to the size of the daily dose, and was longer following administration of divided doses than after administration of a large single dose. Survival time could be prolonged in dogs by ligation of the posterior vena cava. The pathologic changes were much like those observed following irradiation, but the action of $HN_2$ is more rapid and less sustained than that of radiation. The cause of death in most of the dogs could not be explained. In two of the animals it was attributed to septicemia with numerous embolic bacterial abscesses. Dogs receiving $HN_2$ did not have an associated hemorrhagic diathesis.

The pathologic changes in two patients with adenocarcinoma of the rectum

following administration of $HN_2$ were similar to those observed in the rectum of dogs receiving the drug. Administration of intra-arterial $HN_2$ resulted in regression but not eradication of adenocarcinoma in two patients. 14 references. 17 figures. 3 tables.

20. *The Pathology and Growth Behavior of Experimental Tumors Induced by Certain Petroleum Products.* DOUGLAS A. SUNDERLAND, WILLIAM E. SMITH AND KANEMATSU SUGIURA, New York, N. Y. Cancer 4:1232–45, November 1951.

The structure, behavior and metastasis of skin tumors produced by painting the skin of mice with various petroleum products was studied in 90 experiments. The tumors included papillomas, squamous carcinomas, basal-cell epitheliomas and one possible spindle-cell sarcoma. There seemed to be very little correlation between the special type of test material and the structure of the skin tumor. A direct correlation was demonstrated, however, between the total number of tumor-bearing animals produced by a sample and the brevity of the latent period prior to appearance of the tumors, the number of cancers produced, and the brevity of the interval between the first papilloma and the first cancer. No strongly carcinogenic sample was found associated with a long latent period before the appearance of the first tumors, but several weak samples were associated with short periods of latency. This might be ascribed to the high susceptibility of the individual mice. The lymphomas and pulmonary adenomas found in experimental and control mice were believed to be spontaneous. Tumors of the liver, an adenocarcinoma of the colon, and hyperplastic changes found in the mucosa of the stomach and colon are briefly mentioned. Conclusions as to their significance must be postponed until completion of further controlled investigation. 12 references. 24 figures. 2 tables.

21. *A Comparative Study of the Serum Glycoproteins in Patients with Parenchymatous Hepatic Disease or Metastatic Neoplasia.* EZRA M. GREENSPAN, ISRAEL LEHMAN, MORRIS M. GRAFF AND EMANUEL B. SCHOENBACH. Cancer 4:972–83, September 1951.

A comparative study of the serum glycoproteins in patients with parenchymatous hepatic disease or metastatic neoplasia was conducted. The study included determinations of the polysaccharide content of whole serum (P-1), the polysaccharide bound to the total precipitated serum proteins (P-2), the polysaccharide component of the serum mucoprotein (P-3), and the protein (biuretpeptide) component of the serum mucoprotein (M).

Numerous clinical observations have indicated that the glycoprotein content of the serum may be increased in pathologic states associated with increased tissue proliferation or destruction. Among patients with neoplastic disease, exclusive of multiple myeloma, the carbohydrate moieties (P-1, P-2, and P-3) were increased as was the mucoprotein (M). The ratios of P-1, 2, or 3 to M were normal. In uncomplicated hepatitis, portal cirrhosis, and multiple myeloma, the protein component (M) was below normal but the polysaccharide content approximated the

normal range, so that ratios of P-1, 2, or 3 to M were increased above the normal. The reduction in M and the increased P:M ratios in uncomplicated hepatitis and cirrhosis and multiple myeloma could not be attributed to the presence of hyperglobulinemia or selective coprecipitation. The relationship of the mucoproteins to the serum alpha-globulins and their correlation with other indices of liver function are discussed. It appears that the selective reduction in the protein component of serum mucoprotein represents a heretofore unrecognized manifestation of the impairment of protein synthesis which occurs during hepatic insufficiency. 4 figures. 2 tables. 28 references.—*Author's abstract.*

# respiratory diseases

22. *Oral Nonspecific Therapy.* HOWARD B. EMERSON, JR., Tarentum, Pa. Internat. Rec. Med. *164*:651–56, November 1951.

In treating a reported series of 118 patients with chronic infection of the upper respiratory tract, advantage is taken of the ability of certain naturally occurring agents given orally to induce one or the other of the body's two known types of nonspecific reaction. The two types of agents are combined in the treatment. The presumptive cure rate of chronic infection of the upper respiratory tract was 50.5 per cent. The duration of treatment in those in whom presumptive cure was obtained ranged from 5 to 27 weeks. Recognition of the common denominator of allergy and focal infection and the necessity of treatment of both simultaneously is emphasized. 24 figures.—*Author's abstract.*

23. *The Treatment of an Attack of Bronchial Asthma.* ETHAN ALLAN BROWN, Boston, Mass. J. Kansas M. Soc. *52*:529–35, November 1951.

The treatment of bronchial asthma has progressed as far in the last ten years as have the methods of treatment used in surgery, medicine, and their subsidiary fields. A physician who treats acute bronchospasm with an injection of morphine is criminally negligent, and one who limits himself to injecting epinephrine has not only given his patient temporary relief, but done him a real disservice unless he follows this with the other medications known to be necessary to prevent an immediate recurrence.

In the attack, the patient is usually apprehensive, and suffering from the effects of successive "alarm reactions". He is thirsty, hungry, and tired, and in addition shows a sign of hypoxia, cyanosis, and vascular collapse. For adequate treatment, all of these pathologic processes must, when possible, be reversed.

The factors responsible for the patient's condition may not be immediately apparent. If a history can be taken, the physician should question the patient or his attendants as to whether the attack was preceded by such nonspecific factors as pulmonary irritation, due to the inhalation of irritant fumes; or pulmonary infection, fatigue, exertion, or emotional distress. The possibility of reaction to seasonal, environmental, or climatic influences should also be elicited, if possible.

It is well to discover whether the patient has had an unusual exposure to an allergenic food, inhalant, injectant, or drug, all of which help determine the treatment and the prognosis.

Other complications, if present, must be treated in their own right, and those which should be in the forefront of the mind, must include the common cold, paranasal sinus disease, bronchitis, pneumonia, pleurisy, bronchiectasis, and perhaps, with great rarity, obliterative endarteritis of the pulmonary vessels.

The physician should suspect, and also be able to recognize, wheezing as due directly to industrial, chemical, biological, or miscellaneous inhalants; to viral, rickettsial, or parasitic; to neoplasms, primarily or secondarily affecting the lung; to blood diseases associated with dyspnea, as anemia and perhaps leukemia; to generalized conditions, as lupus, *periarteritis nodosa*, Loeffler's syndrome, tropical eosinophilia, cystic disease of the pancreas, and rheumatic fever.

In the lung, not only must the conditions listed be considered, but also perhaps others associated with pulmonary fibrosis and the circulatory disturbances, as associated with pulmonary edema, with or without obstructions, lesions, or infections; or a hyperventilation syndrome, psychologically induced, must be kept in mind.

For the treatment of bronchial asthma in children, the original paper should be consulted. In the adults there are four states, or grades, of bronchial asthma. In the early stages of the condition, there is a respiratory oppression associated with difficulty in deep inspiration, the pain being mild, lasting for hours, and not interfering with activity. The chest is almost free of signs at this stage.

In the next degree of bronchial asthma, the patient suffers from what appears to be an allergic tracheitis, with a constant cough and dyspnea. Examination of the lungs proves the presence of subclinical sibilant, and sonorous rales. It is in the third stage that this dyspnea becomes more marked, and troublesome, as well as expiratory in type, the wheezing disappearing with rest and responding readily to injection, oral, or inhalant medication.

In the fourth stage, the patient has "intractable asthma", labelled as "status asthmaticus".

In mild cases, and while studies are in progress, potassium iodide in doses of 15–30 drops taken three times daily may be sufficient. For simple wheezing, the various combinations of ephedrine, phenobarbital, aminophylline, such as Luasmin, Quadrinal, and others may satisfactorily relieve the symptoms.

For the more seriously ill patient, epinephrine (1:1000) may be injected subcutaneously in doses of 0.2–0.5 cc. or inhalation of the 1:100 solution may be used. If ineffective, 0.5–1.0 cc. of epinephrine (1:1000) can be given intravenously in 1000 cc. of glucose saline.

Aminophylline used intravenously can be injected, in a 0.25–0.5 Gm. dose at a rate of 2.0 cc./minute using the 20 cc. solution. This can be repeated two or three times every 24 hours.

The safest sedative medication consists of sodium bromide, or triple bromides, in the 5–15 gr. dose, combined with chloral hydrate in the 5–10 gr. dose in simple

syrup or Iso-elixir. In "Wet asthmatic" patients, Demerol in the 100 mg. dose and scopolomine hydrobromide in the 0.3 mg. dose has been used. With more severe patients, gas therapy may be required using various combinations of oxygen: oxygen and air, oxygen and helium, or oxygen and carbon dioxide.

More severely affected patients may require isotonic glucose, in 1000–3000 ml. doses with each 24 hours, and hypochloremia, and hypopotasinemia must be corrected. In some patients sodium racemic lactate may be necessary. Rare patients require plasma. Cortone and ACTH, although they are frequently used, are not part of the present publication.—*Author's abstract.*

24. *Observations on Nethaphyl in Bronchial Asthma.* I. FOND, Chicago, Ill. Illinois M. J. *100*:7–9, July 1951.

Searching for a preparation that would give prompt and prolonged relief from an attack of bronchial asthma, with the least stimulating effect on the central nervous system, Nethaphyl® was administered to 60 veterans who came under treatment at the Allergy Clinic of the Veterans Administration of Chicago. Nethaphyl® is a combination of Nethamine Hydrochloride $\frac{3}{4}$ gr., Butaphyllamine® 2 gr., and Phenobarbital $\frac{1}{4}$ gr. The intermittent administration of Nethaphyl was continued in each patient for 3 to 6 months.

All patients obtained relief beginning 20 to 60 minutes and lasting from 3 to 12 hours after administration. Side reactions were complained of by ten patients, but these were transitory and were evidenced only during the first few days of medication. In no case was it necessary to discontinue administration of the preparation.

Most patients stated that Nethaphyl®, taken as soon as symptoms began to appear, in most instances abated the attack of asthma. However, it had no effect once a severe attack of asthma developed.

Complete blood counts and urinalyses were made on each patient prior to the administration of Nethaphyl® and at the conclusion of the period of observation. No particular changes were noted in the blood and urine. 1 table.—*Author's abstract.*

25. *Eosinopenia in Status Asthmaticus. A Report of Two Cases.* PAUL B. JENNINGS, Trenton, N. J. J. M. Soc. New Jersey *48*:507–09, November 1951.

Eosinophilia has long been known to be associated with allergy appearing in high concentrations in both peripheral blood and at the site of the allergic reaction. The exact function of this cell is not fully understood, but recent investigation has shown a close relationship to histamine and Charcot-Leyden crystals as well as pointing out the eosinopenia resulting from a variety of modes of stress and the use of eosinophil level as a measure of adrenocortical function.

Since patients suffering from severe *status asthmaticus* are undergoing marked stress, observations on the eosinophil level of two such patients proved interesting. Both patients who originally showed an eosinophilia demonstrated a marked fall in the circulating eosinophil level during the acute, nearly fatal bout of *status*

*asthmaticus*, probably as a result of an increased production of adrenocorticoids. These findings, coupled with the rise in eosinophils which preceded the fall, are used as evidence to support the hypothesis that during stress eosinophils are mobilized from the bone marrow and collect at the shock organ.

It also is pointed out that, while both patients had been receiving epinephrine for years and one was treated with ACTH, eosinophilia still persisted. However, when these patients were subjected to severe stress and impending death, the healthy pituitary and adrenal glands apparently discharged hormones far in excess of the "therapeutic doses" of ACTH, cortisone, and epinephrine that are ordinarily used. 2 tables.—*Author's abstract.*

26. *Some Effects of Adrenocorticotropic Hormone and Cortisone on Pulmonary Function of Patients with Obstructive Emphysema.* DANIEL S. LUKAS, New York, N. Y. Am. Rev. Tuberc. *64*:279–94, September 1951.

Pulmonary function was studied before and during administration of adrenocorticotropic hormone (ACTH) and cortisone in 9 patients with various types of chronic lung disease. Subjective and objective improvement, sometimes dramatic, occurred in those patients whose disease was secondary to or complicated by bronchiolar obstruction and was minimal or absent in those without obstruction. This observation, together with the pattern of change in pulmonary function, suggested that ACTH and cortisone exerted a sustained bronchodilating action. The effect of these agents on the bronchial tree was greater than the action of conventional bronchodilators in at least 2 patients with chronic obstructive emphysema, and was helpful in revealing the true extent to which their functional impairment could be attributed to bronchiolar obstruction rather than to permanent anatomic changes. In these patients, improvement in maximum breathing capacity, vital capacity, oxygenation of arterial blood and reduction of residual volume was dramatic. Further depression of gas exchange encountered in a patient with *cor pulmonale* was thought to reflect the development of edema of the alveolar membrane. Such side effects are hazards of ACTH and cortisone administration in far advanced chronic lung disease. 13 references. 4 figures. 7 tables.—*Author's abstract.*

27. *Delays in the Diagnosis of Tuberculosis from the Incautious Use of Antibiotics.* WILLIAM H. OATWAY, JR., Los Angeles, Calif. Arizona Med. *8*:25–28, July 1951.

Forty per cent of the tuberculous patients in a small Los Angeles Sanatorium gave a history of antibiotic treatment for respiratory infections before admission. The infections were called by various names, often including the word "virus". The diagnosis was rarely confirmed by x-ray or bacterial studies. Some of the patients were known to have had tuberculosis in times past. A few cases were missed by a wrong interpretation of x-rays.

All of the patients were prevented from receiving proper care, for weeks to many months, by the failure to exclude tuberculosis, until after one or more trials of one or more antibiotics.

Free use of chemotherapy is an alluring routine for both patient and physician. The hazards of such usage have been predicted and now seem evident. The physicians, at least, should be more careful and the drug manufacturers more cautious in their claims. A "broad spectrum" is no substitute for an adequate examination.

Quite a few of the undiagnosed lesions were discovered in a coincidental chest x-ray survey in the community. This emphasizes the value of such surveys of x-rays and fluoroscopy in general, and of the need for inexpensive facilities.

The drugs may give a false sense of security if symptoms decrease. All of the reported cases were infectious on admission, however, and some of them had become nearly untreatable because of the delay.

It is probable that this small experience can be duplicated through the country. If so, it is a genuine hazard of considerable proportions.—*Author's abstract.*

28. *Streptomycin in the Therapy of Tuberculosis.* WILLIAM C. KEETTEL, Iowa City, Iowa. Am. J. Obst. & Gynec. *61*:1382–85, June 1951.

During the last year, there have been several reports dealing with the result of streptomycin therapy in tuberculosis of the female genital tract. Inasmuch as previous reports have dealt with less extensive involvement, it seems advisable to report the following case.

This is a case of extensive vaginal, cervical, and endometrial tuberculosis which was proven by biopsy and was treated with two Gm. of streptomycin daily for 87 days without untoward reactions. Audiogram showed no hearing loss. Following the cessation of streptomycin therapy, the patient had a long period of amenorrhea, but there was a complete regression of the tuberculosis, so that on repeated endometrial biopsies and cervical biopsies, there was no evidence of involvement. One year after the completion of the streptomycin therapy, the patient started menstruating and has now been menstruating regularly. Thus, streptomycin seems to be a valuable adjunct to our present armamentarium in the treatment of tuberculosis of the female genital tract. It is still too early to state whether genital tuberculosis in the female can be cured by such therapy or whether it should be used only in conjunction with the surgical approach. 2 references. 4 figures.—*Author's abstract.*

29. *The Tuberculostatic Activity of Terramycin.* G. L. HOBBY, Brooklyn, N. Y. Am. Rev. Tubere. *63*:434–40, April 1951.

Terramycin is a new antimicrobial agent which has been investigated widely during the past year. Its possible value as an antituberculous agent was first mentioned in an early communication from this laboratory in which it was reported that terramycin is capable of inhibiting the growth of both streptomycin-sensitive and streptomycin-resistant strains of micrococcus tuberculosis *in vitro.* Subsequent reports by these investigators and by Steenken and Wolinsky confirmed these observations and indicated further that terramycin is capable of suppressing tuberculous infection in experimentally inoculated mice and guinea pigs.

The present report was designed to clarify the available evidence concerning

the antituberculous activity of this new antibiotic. Data are presented which illustrate the fact that 4 to 16 μg. of pure terramycin per ml. of medium are sufficient to inhibit growth of both streptomycin-sensitive and streptomycin-resistant strains of tubercle bacilli under the experimental conditions used. Subinhibitory concentrations of terramycin, equivalent to one-fifth to one-tenth of the amount required for inhibition of growth, significantly decrease the concentrations of streptomycin, viomycin, and aureomycin necessary for inhibition of growth. In a rapidly progressing infection in mice, infected by the intracerebral route with human tubercle bacilli, a dosage equivalent to 8.6 mg. of terramycin, per 20 Gm. mouse per day was sufficient to increase the average survival time from 24 days among the untreated control animals to 120 days in the treated series. Lower dosages of the sodium salt of terramycin, equivalent to 1.1 to 2.2 mg. per day, were sufficient to cause an approximately three- to fourfold increase in survival time. Terramycin, both in its amphoteric form and as its sodium salt, was effective therefore in suppressing this infection. Preliminary observations suggested that terramycin hydrochloride, when administered subcutaneously, may be slightly less effective.

The development of streptomycin and the recognition of its value as a chemotherapeutic agent in tuberculosis arouses interest in the evaluation of the potentialities of other antibiotics in the treatment of this infection. The frequency with which organisms resistant to the action of streptomycin emerge from otherwise sensitive strains has remained a serious drawback to its use, and the need for other antituberculous agents capable of acting upon streptomycin-resistant strains is well recognized. The activity of terramycin *in vitro* and *in vivo* against streptomycin-resistant strains of tubercle bacilli and its low toxicity, combined with its ability to exert an apparent synergistic effect upon other antituberculous agents at least *in vitro*, suggest that this agent may be of value in this regard. 21 references. 5 tables.—*Author's abstract.*

30. *Electrocardiographic Changes Accompanying Pulmonary Collapse Therapy and Thoracic Surgery.* MAX WEINSHEL, IRVING MACK, ARMOND GORDON, AND GORDON SNIDER, Chicago, Ill. Am. Rev. Tuberc. *64*:50–63, July 1951.

A study of the electrocardiographic changes occurring before and after pulmonary collapse therapy and various types of thoracic surgery demonstrates that most of these changes are those reflecting changes in "electrical" position. These were readily correlated with similar changes in anatomic position as evidenced by roentgenographic control.

In both right and left pneumothorax, the "electrical" position tended to become more vertical. The transition zone in the chest leads showed a tendency to be shifted to the left in patients with right pneumothorax. In left pneumothorax, the amplitude of QRS in the chest leads became diminished.

After either right or left pneumonectomy, the "electrical" position of the heart became more horizontal. The shift in transition zone in the chest leads was seen to depend on the interval of time that had elapsed following the surgical procedure.

After either right or left thoracoplasty, there was a slight tendency for the "electrical" position of the heart to become more horizontal.

In pneumoperitoneum, the "electrical" position of the heart became more horizontal. The transition zone in the chest leads became displaced to the right. 19 references. 6 figures. 1 table.—*Author's abstract.*

# cardiovascular diseases

31. *Mumps Myocarditis.* M. Z. IRVIN, Tacoma, Wash., T. H. BACHARACH, AND ROSCOE L. PULLEN, New Orleans, La. Northwest Med. *50*:583–85, August 1951.

A twenty-seven-year-old male with acute orchitis, but no parotid swelling, had electrocardiographic evidence of myocarditis. Complement fixing antibodies were high. Use of this reaction will reveal cases of mumps without parotitis. Until the reaction is more widely employed, the true incidence of atypical mumps cannot be stated. 12 references. 2 figures.—*Author's abstract.*

32. *Temporal Arteritis: Report of a Case with ACTH Therapy.* WENDELL M. TATE, Peabody, Kan. and JAMES A. WHEELER, Newton, Kan. J. Kansas M. Soc. *52*:374–77, August 1951.

A case of temporal arteritis is presented and a review of the literature from 1890 when the disease was first described by Jonathan Hutchinson in England, to the present time, is given. Approximately 85 cases have been reported. The reports in the literature indicate that temporal arteritis is a pathologic process involving not only the temporal vessels, but the process has been found at autopsy to involve the retinal, subclavian, renal, carotid, coronary, femoral, occipital, brachial and cerebral vessels. Clinically the red, swollen, nodular, painful temporal arteries and the severe, persistent headaches, with marked systemic reactions, such as general malaise, anorexia, loss of weight, low grade fever, mental confusion, vomiting, and marked weakness occurring at about 65 years of age, is noted. The pathologic picture is fairly constant with the microscopic picture of a periarteritis and arteritis. The media shows the greatest changes with replacement of the muscle by collagen, necrosis, and hemorrhage. Multinuclear giant cells may be seen. The cause of temporal arteritis is unknown.

Most of the cases diagnosed as temporal arteritis or cranial arteritis, according to the literature, have recovered in a month to twenty months. About 10 per cent have associated eye symptoms and about half of these have been left blind in one or both eyes. No specific satisfactory treatment is known; however, procaine block of the nerves of the temporal vessels and biopsy severing of the vessels have proven most successful to date. A case of temporal arteritis occurring in a 75 year old white female is presented, who, until treatment was started with adrenocorticotropic hormone (ACTH), was growing progressively worse. ACTH was given in 10 mg.

dosage or 1 cc. every 6 hours the first fourteen days, with dramatic relief of all symptoms. The next fifteen days the patient was given 10 mg. or 1 cc. of ACTH every 8 hours. The next ten days only 5 mg. or ½ cc. of ACTH every 12 hours was apparently necessary. The ACTH was discontinued for 8 days, but as symptoms were returning, 1 cc. or 10 mg. every 12 hours was again started, with complete relief of symptoms for twenty-three days when it was decreased to 1 cc. or 10 mg. once daily for three weeks and then discontinued entirely with complete recovery. The total dosage of ACTH was 2,100 mg. To the authors' knowledge, this is the first report of ACTH being used in this disease. 23 references.—*Author's abstract.*

33. *The Heart in Anemia.* CALVIN F. KAY, Philadelphia, Pa. Am. Pract. 2:587–89, July 1951.

Severe anemia may cause a specific pathologic type of organic heart disease as a result of prolonged myocardial anoxia. Lesser grades of anemia may cause symptoms, especially after exertion, which may appear to be of intrinsic cardiac origin. These symptoms result from an increased volume and velocity of the circulation and resemble those of neurocirculatory asthenia and hyperthyroidism. The symptoms, together with murmurs, gallop sounds, and electrocardiographic abnormalities, may lead to an erroneous diagnosis of intrinsic heart disease. In the presence of these findings, even when the anemia is clearly recognized, the exclusion of coincident intrinsic heart disease may be very difficult. This is particularly the case in sickle cell anemia, where fever, pains in the extremities, and a presystolic murmur may strongly suggest rheumatic fever.

The unfavorable influence of anemia in the presence of intrinsic cardiovascular disease should be clearly implied from a recognition of the effects of anemia upon the otherwise normal heart. An increased cardiac output is demanded of the already burdened heart. Angina and intermittent claudication may be severely aggravated, because the diseased vessels cannot dilate, as in the normal, to permit the necessary increase in volume of blood flow to the tissues. The unwholesome relation of anemia and cardiovascular disease has been abundantly demonstrated in clinical practice. 10 references.—*Author's abstract.*

34. *Experimental and Human Atherosclerosis: Possible Relationship and Present Status.* MAURICE BRUGER, ELLIOT OPPENHEIM, New York, N. Y. Bull. N. Y. Academy Med. 27:539–59, September 1951.

The subjects of experimental cholesterol atherosclerosis and human atherosclerosis have been reviewed and their possible relationship discussed. Analysis of published data permits certain major conclusions: (a) The precipitation of cholesterol in the intima is accelerated by increased concentrations in the plasma of cholesterol, chylomicrons and macromolecular cholesterol aggregates of definite dimensions and by increased filtration pressure (hypertension) and generalized obesity; it is conceivable that some, if not all, of these atherogenic factors increase intimal permeability for cholesterol. (b) The precipitation of cholesterol in the intima is inhibited by such agents as estrogenic hormones, intravenous detergents,

iodides, desiccated thyroid, and thiocyanates; it is believed that these antiatherogenic factors either maintain the colloidal stability of cholesterol in the plasma by increasing the concentration of plasma phospholipids or decrease intimal permeability for this sterol; the reputed antiatherogenic activity of lipotropic factors such as choline, inositol and methionine has not been definitely established. (c) The prolonged consumption of foods low in fat and free of cholesterol may inhibit cholesterol deposition in the intima by decreasing the concentration in the plasma of cholesterol, chylomicrons, and macromolecular cholesterol aggregates. 106 references. 1 figure. 3 tables.—*Author's abstract.*

35. *The Phenomena of Chylomicrons in Fat Absorption and Arteriosclerosis.* R. NECHELES, Chicago, Ill. Am. J. Digest. Dis. *18*:229–31, August 1951.

A review of previous work with chylomicrons and a report on extension of the work in a new series of young and old individuals are presented. A standard fat meal was administered by mouth and the chylomicron counts on venous blood were performed repeatedly. The previous findings of much higher and prolonged chylomicronemia in old people than in young ones were confirmed. It was found that smoking and physical exercise raised the chylomicron counts. Chemical analysis of chylomicron fat obtained from a blood bank showed that it contains 10–12 per cent of steroids, of which 80 per cent appear to be cholesterol. Of the cholesterol 65 per cent was esterified. 11 references.—*Author's abstract.*

36. *Effect of Small Doses of Heparin in Increasing the Translucence of Plasma During Alimentary Lipemia: Studies in Normal Individuals and Patients with Atherosclerosis.* W. J. BLOCK, JR., F. D. MANN, AND M. W. BARKER, Rochester, Minn. Proc. Meet. Mayo Clin. *26*:246–49, June 1951.

Since Hahn's observation in 1943, it has been known that intravenous heparin increases the translucence of plasma during alimentary lipemia. In view of recent reports as to the possible relationship between atherosclerosis and the physicochemical state of blood lipids, this study was conducted to learn whether or not this peculiar effect of heparin occurred in equal degree in normal individuals and individuals with atherosclerosis. Included in this study were tests on 20 normal females, 23 normal males, and 27 atherosclerotic males (*arteriosclerosis obliterans* and coronary sclerosis). Each was given 3 mg. of heparin intravenously three hours following ingestion of a standard fat meal. Normal males developed a decrease in the translucence of plasma following the fat meal, which was significantly greater than that developed by normal females of the same age group. Male atherosclerotic patients tended to show much less clearing of plasma following heparin during alimentary lipemia than did normal male and female subjects.

The data appear to show a true relationship between atherosclerosis and resistance to clearing of lipemic plasma by heparin. This resistance in this group of patients could be an expression of an abnormal inhibition or neutralization of heparin or of a basic abnormality in the state of the plasma lipids, or both.

Whether this finding will prove to be of diagnostic, prognostic, or therapeutic significance will depend on future studies. 8 references. 2 tables.—*Author's abstract.*

37. *Electrokymographic Studies of Ventricular Border Movements in Aortic Insufficiency and Ventricular Hypertrophy.* EDWARD PHILLIPS, Los Angeles, Calif. Ann. West. Med. & Surg. 5:534–38, June 1951.

The electrokymogram shows a pathognomonic abnormality in aortic insufficiency consisting of shortening or abolition of the isometric relaxation phase. The isometric relaxation phase was less than 0.06 second in 28 of 50 of the author's cases of aortic insufficiency. The abnormally short or absent isometric relaxation phase is due to the fact that regurgitation through the incompetent aortic valve begins immediately after ventricular ejection, and ventricular filling therefore begins even before the auriculoventricular valves open.

The isometric relaxation phase may be prolonged in ventricular hypertrophy from any cause. The isometric relaxation phase was prolonged (greater than 0.18 second) in 43 of the author's 100 consecutive cases of left ventricular hypertrophy. These patients had compensated hypertensive, coronary arteriosclerotic, or rheumatic (aortic stenosis) heart disease. The prolongation of the isometric relaxation phase in ventricular hypertrophy is best explained on the basis of Wiggers' findings that the first mechanical manifestation of muscular fatigue is an increase in the duration of contraction with a delay in the onset of relaxation. However, there must be other causes of prolonged isometric relaxation phase, inasmuch as the prolonged isometric relaxation phase may return to normal *after* heart failure appears. Not a single instance of prolonged isometric relaxation phase was observed in 12 patients with congestive heart failure. Three patients with previously prolonged isometric relaxation periods showed a significant shortening of the isometric relaxation phase after congestive failure occurred.

Digitalization may shorten the isometric relaxation phase. Ten patients with hypertensive heart disease and left ventricular hypertrophy, who showed prolongation of the isometric relaxation phase, but who were without evidence of cardiac decompensation, were completely digitalized. Four of these patients showed a decrease in the duration of the isometric relaxation phase to normal. This suggests that digitalis has an intrinsic effect on the mechanical as well as the electrical systole of the heart. 15 references. 4 figures.—*Author's abstract.*

# gastrointestinal diseases

38. *Gastric Ulcer. Diagnostic Studies in 100 Cases.* JAMES A. HAGANS AND MALCOLM C. MC CORD, Fort Wayne, Indiana. Am. J. Digest. Dis. *18*:335–37, November 1951.

The authors assembled a series of 100 cases of gastric ulcer from the files of a veterans' general hospital and included all cases which had the presence of a gastric ulcer satisfactorily established by roentgenologic study, gastroscopic examina-

tion, or direct specimen examination of surgical or autopsy material, and in addition, a sufficiently thorough clinical and laboratory evaluation to be useful in their study. They then attempted to analyze and tabulate pertinent points in the history, laboratory findings, x-ray studies and gastroscopic examinations, to see if any of the usual tests performed on such patients were of any value in differentiating the benign from the malignant gastric ulceration. Their findings supported the view that the usual criteria in fairly routine use are not only of no value in differentiating the benign from the malignant ulcer of the stomach, but may in an individual case actually be misleading. Finally, then, they suggested that the problem in management presented by the patient with a gastric ulcer had best be met either by immediate surgical resection, or, more conservatively, by a closely supervised trial of strict medical treatment with repeated studies, and thence surgical intervention only in those patients who respond poorly or who develop a recurrence of the lesion. 2 references. 6 tables.—*Author's abstract.*

39. *Chemotherapy as Prophylaxis Against Secondary Intestinal Tuberculosis. A Report of 150 Autopsies.* IVAR KALLQUIST, New York, N. Y. Am. Rev. Tuberc. *64*:430–41, October 1951.

The findings in the many autopsy studies carried out before the introduction of chemotherapy show that intestinal tuberculosis was a very common complication of pulmonary tuberculosis. In a previous report (Am. Rev. Tuberc. 1950, *61*:621) on the therapeutic action of para-aminosalicylic acid (PAS) on secondary intestinal tuberculosis, the writer expressed the opinion that this effect is so excellent that the prognosis *quoad vitam* is largely dependent on the outcome of the underlying pulmonary disease. Other writers have reported similar favorable results with streptomycin and thiosemicarbazone. It was felt that the proof of the writer's assumption was to be sought in the postmortem findings in the gastrointestinal tract of patients who, despite chemotherapy, died of pulmonary tuberculosis. The study was limited to the three-year period 1948–1950, so as to exclude any significant tendency towards a general decline in the frequency of the complication.

During this period there were 234 adult deaths from pulmonary tuberculosis. Of these patients 62 had, and 172 had not, received treatment with antimicrobial agents. Forty-six (74.2 per cent) of the treated cases were examined postmortem as against 104 (60.5 per cent) of the untreated cases. The comparative smallness of the treated group was due to a sharp decline in the death rate at the hospital during the period of the study. Of the 46 treated patients, 20 had been given PAS alone, 9 streptomycin alone and one thiosemicarbazone alone. The remaining 16 had received two or all of the preparations.

Only macroscopic ulcers were considered. Tuberculous lymph nodes, tuberculous peritonitis, preulcerative reddening of the mucosa, etc. were not included in the analysis.

*Results:* Of 104 cases without chemotherapy, 41 or 39.4 per cent were found to have secondary intestinal tuberculosis.

In the 46 cases with chemotherapy, the figure was 7, or 15.2 per cent. In 37 of these

patients, chemotherapy had been discontinued less than six months prior to death, and of these only 2 or 5.4 per cent had intestinal involvement. The lesions in the untreated cases were much more extensive than those in the treated cases. Serpiginous ulcers were found in 63.3 per cent of the enterocolitis cases in the former group and in only 14.3 per cent of the latter.

The study also showed that the frequency of secondary intestinal tuberculosis in untreated male cases was much greater (46.3 per cent) in patients less than fifty years of age than in older male patients (16 per cent). The number of women older than fifty was too small to permit such a comparison.

Statistical analysis of the frequency figures showed a significant difference for men less than fifty years of age; the figures for women less than fifty lay well within the bounds of statistical probability.

Antimicrobial therapy was thus found to have effected a considerable decline in the frequency of ulcerative enterocolitis in fatal phthisis. Agents specific for *M. tuberculosis* have thus a prophylactic action against secondary intestinal tuberculosis. 14 references. 6 tables.—*Author's abstract.*

40. *Chronic Ulcerative Colitis—Clinical and Bacteriologic Response to Aureomycin.* MICHAEL H. STREICHER AND ROBERT KNIERING, Chicago, Ill. Am. J. Digest. Dis. *18*:231–34, August 1951.

As in all scientific pursuits in clinical medicine, one invariably becomes tenaciously attached to the study of some entity yet unconquered. At this writing, after many years physicians are still searching for specific treatment for one of the most dreadful diseases of the abdomen, chronic ulcerative colitis. Until the early years of the twentieth century, all reports on the subject were very discouraging. It has been the opinion of most gastroenterologists that the treatment of colitis was limited to that of the specific forms of ulcerative colitis and that the diagnosis of the nonspecific form was based on the existence of colon ulcers with negative bacteriologic observations with extensive anatomic changes of the colon.

In 1926, Streicher and Kaplan began extensive clinical and experimental studies on ulcerative colitis and reported that all bacteria present in the colon during the course of this disease were responsible causative factors.

It is quite obvious that, in addition to the presence of severe infection, there is associated a marked loss in weight, diarrhea, cramping in the abdomen, and a loss of body fluids, so that the nutritional reserves of the individuals are rapidly depleted. One also encounters the problem of remissions or recurrent exacerbations of ulcerative colitis.

The introduction of therapy with the sulfanilamide and its derivatives was hailed as a step in the right direction and, while miraculous results were recorded at the onset, it was finally established that the specific action exhibited by certain sulfonamides was limited in scope and that the action was bacteriostatic against the secondary bacterial invaders.

A constant and continued search for an antibiotic that would be effective against a wide variety of bacteria, both aerobic and anaerobic, gram-positive and gram-negative resulted in the discovery of aureomycin by Duggar.

*Procedure of Study.* Fifty patients afflicted with chronic ulcerative colitis were employed in this study; of these 18 were males and 32 females. All were studied clinically and proctoscopically. Aureomycin (thrice recrystallized) was administered orally to each patient in doses varying from 3 to 6 capsules (250 mg. each) daily. The majority of the patients were hospitalized for two weeks and controlled during the experimental trial. Studies of levels in the blood, urine, and stool were determined daily. Bacteriologic studies were made before and after treatment.

*Results.* The bacteriologic response in the stool and oral administration of aureomycin is significant in that the B. coli count, the staphylococcus aureus, streptococcus alpha, streptococcus beta and streptococcus gamma counts are all decreased progressively and correspondingly.

*Clinical Studies.* This study was carried on for one year. Of the 50 patients treated orally with aureomycin, 32 were female and 18 were male; of these 23 were in the chronic stage and 27 in the acute stage. The majority of the group showed improvement with oral administration of aureomycin in doses of 3 to 6 capsules (250 mg. each) daily. The impression obtained is that the patients are benefited to the extent that the cramping in the abdomen subsides, that the discomfort in the abdomen is alleviated, and that the number of evacuations are reduced. A small percentage of the patients have been disturbed by nausea and occasional vomiting after oral intake of aureomycin; some complain of burning on urination or headache; however, this varies with the particular preparation used. The stools become more formed, not odorless and the blood in the stool is reduced considerably; the color also changes to a lighter yellow.

The entire group was studied proctoscopically after treatment, but the changes are not pronounced enough to evaluate accurately. In general, one may say that, on direct visualization, there is evidence of some improvement in the resistance of the colon mucosa to ulceration upon direct trauma.

While aureomycin has been found therapeutically to be active against a broad spectrum of bacteria, it is recognized that organisms vary in their susceptibility to this antibiotic. Oral aureomycin is absorbed very readily and therefore is well adapted for ambulatory patients.

It has been found that aureomycin is most effective when used in the presence of actively reproducing bacteria and that bacterial resistance to this antibiotic is not developed easily. These properties of aureomycin are evaluated to a great extent in the treatment of chronic ulcerative colitis.

There is conclusive evidence of bacterial response to aureomycin demonstrated in this group of patients with ulcerative colitis; there is a gradual and progressive decrease in the numerical count of the bacteria studied; this coupled with a general clinical improvement of these patients over a period of 14 days would indicate that aureomycin administered orally is beneficial in chronic ulcerative colitis. Since ulcerative colitis is a disease process of prolonged duration, interpolated by

remissions and exacerbations, administration of any form of medication would of necessity extend over prolonged periods; any antibiotic therefore which is employed in the management of ulcerative colitis should possess properties free of toxic effects which would render the agent suitable in this requirement.

In our studies, we were also interested in determining whether or not aureomycin is primarily bacteriostatic or bactericidal; in directing our studies beyond 14 days, this question too, would be more easily qualified. 17 references, 3 tables.—*Author's abstract.*

11. *The Matting Syndrome.* HOWARD MAHORNER, New Orleans, La. New Orleans Med. & Surg. J. *104*:17–22, July 1951.

During a five-year period from January 1946 to January 1951, 58 patients underwent 60 operations during the course of which findings indicated acute or complete obstruction in 36 instances and chronic or partial obstruction in 24. Some of the latter were recurrent, partial obstructions. Among the acute cases, the diagnosis was intestinal obstruction either of a nonspecified or a specified type in 32 of the 36 instances. There were 14 children 4 years of age or younger in the entire group.

A characteristic "matting syndrome" is making appearance much more frequently. Such patients have been operated upon before, usually for pelvic trouble. Several years after the previous operation, this group of patients begins to have pain and soreness in the right lower abdomen. A vague indefinite sensation of nausea may accompany the attacks of soreness; the attacks seldom get acute; and at first they are intermittent. Persistence of soreness is a characteristic feature. Constipation is associated. They do not look sick and the examination may be negative except for a mild amount of tenderness in the region of the old wound, and a sensation of an indefinite mass or resistence in that area. Gastrointestinal series, even when the roentgenologist has been instructed to take roentgenograms for small bowel stasis, will be reported negative. These patients should be carefully evaluated for emotional and functional factors and usually they are found to be sound and not unstable. The objective findings at operation are always more or less true to a form and characteristic in their appearance. The omentum and small bowel are adherent to the abdominal wall in the region of the wound. The omentum is thickened and scarred and indurated and in some instances is actually edematous. It is heavy and instead of being a fine veil of soft fat, it is thick and hard in consistency. In addition to this, it is firmly adherent to one or more loops of bowel and the bowel is adherent to the adjacent intestine and, most important of the findings, which proves the legitimacy of the diagnosis, the small intestine proximal to this area is dilated and hypertrophied so conclusively that everyone at the operating table agrees that at least this evidence of partial obstruction is present in spite of a negative roentgenographic examination.

Because of numerous advances modifying its course, the surgical management of intestinal obstruction is changing radically. In the preoperative phase, antibiotics, blood transfusions, intestinal decompression, and fluid and electrolyte replacement all help to make the patient look much less sick than he actually may

be. This is particularly true in strangulated obstruction. Twice during this series, the author waited; once a period of twenty-four and again a period of twelve hours with the patient under observation, receiving antibiotics, until at operation the bowel was found to be gangrenous, perfectly black. The patients did not look very sick; they were being decompressed and prepared for operation. In both of these instances, the patients fortunately recovered, but such examples emphasize how seriously delays may jeopardize a favorable outcome. When the diagnosis is made, operation should be done promptly. Decompressive measures are not indicated over a long period of time, a few hours being all that is necessary to get a patient into proper condition in most instances of acute intestinal obstruction. Even in the absence of severe tenderness, strangulation is a possibility. A lesson learned from such findings at operation is not to delay, or to be satisfied with the relative comfort obtained by decompression with the Miller-Abbott tube, and also, that a false sense of security may be suggested by absence of toxemia, which in reality is only suppressed in its systemic manifestations by antibiotics. At operation, the entire gastrointestinal tract should be carefully inspected, then whatsoever technical procedure is indicated should be carried out. One must remove the bowel from the abdomen without fear of the difficulty of replacing it even though it is badly distended. One must be absolutely sure that the obstruction has been found and obviated. If necessary, resection of the intestine should be instituted.

If the bowel is tremendously distended, decompression by insertion of a suction tip into the bowel is not only permissible, but probably is a technical measure of advantage. A further technical method of value is the employment of enterostomy. In severely obstructed cases with peritonitis, in order to diminish the prolonged necessity of using an indwelling transesophageal gastric decompression tube, one, two, or three enterostomy tubes were put in at various levels in the small intestine. An enterostomy tube proximal to an anastomosis may be a life-saving measure, and it always should be employed when an anastomosis is made. In the cases of chronic intestinal obstruction with matting syndrome, one of the very important procedures is to remove the entire omentum.

Resection of the intestine is indicated, not only when there is strangulation with evidences of nonviability, but also in the chronic cases where there is matting and severe adhesions. The latter type of case was formerly managed by separating all adhesions carefully and sometimes by employing a substance such as amniotic fluid, papain, or heparis in preventing their recurrence. But this type of therapy has not been corroborated by reports in the literature to substantiate its value. A far better idea is to resect adherent snarled loops of bowel. Four of the patients operated upon died. Two of these were infants with congenital obstruction; one was a seven-month premature twin with an atresia at the upper end of the jejunum. A duodenojejunostomy was accomplished and, although after operation air progressed into the distal loop, the baby was too weak, apparently, to eat and to propel the contents along the distal segment. A second newborn infant died after duodenojejunostomy for an obstruction of the distal duodenum, from what was thought to be an aspiration pneumonia. Two adults died. One had been operated upon previously for intestinal obstruction. A complete total multiple polyposis of the entire

small bowel was found. A fourth patient developed intestinal obstruction following an abdominoperineal resection for a carcinoma of the rectum and died. It is to be noted, that out of 16 cases, in which intestinal resections or anastomoses were done, only 2 died. There were 3 patients in whom anastomoses were made for congenital obstructions. In 13 instances in which resections were done in the face of intestinal obstruction, all survived. 1 reference. 2 tables.—*Author's abstract.*

42. *Transient Disturbances of Consciousness in Hepatic Cirrhosis.* A. G. W. WHITFIELD AND W. MELVILLE ARNOTT, London, England. Brit. M. J. 4739:1051-56, Nov. 3, 1951.

Three cases of hepatic cirrhosis are described in which transient attacks of unconsciousness occurred. The attacks were not cholemic in the ordinary sense in which that term is used, since between the attacks the patients were mentally alert and normal and led active and useful lives. The condition was mentioned by Osler in 1892 but has not since received much attention in the medical literature and does not appear to be widely recognized.

The first case was a woman of 48 with ascites and leg edema, a hard irregular but not enlarged liver, grade one splenomegaly, esophageal varices and multiple spider nevi. Her liver function tests showed evidence of gross parenchymatous liver damage and her blood a slight macrocytic anemia. For eighteen months before death she suffered transient attacks, usually of about 24 hours duration, in which she became stuporous but consciousness was not completely lost. During the attacks no neurologic or cardiovascular abnormality could be detected and the blood sugar was normal. Electroencephalography, during attacks, however, showed a continuous dominant rhythm of 3–6 cycles per second and phase reversal at the parietal and temporal electrodes on both sides. Between the attacks, she was alert and carried out her normal household duties. Autopsy revealed gross multilobular hepatic cirrhosis, splenomegaly and esophageal varices.

The second case was a woman of 66 with an enlarged hard liver and splenomegaly. Liver function tests showed gross parenchymatous liver damage and the blood count a slight macrocytic anemia. For four months before death she had attacks of unconsciousness (with fever) which were sometimes complete and at other times only amounted to stupor. During these she was incontinent and had to be fed through a Ryle's tube. Nothing could be found to explain the attacks, but during them electroencephalography showed high voltage delta discharges in all leads and phase reversal in the temporal lobes on both sides. For a time, she continued to lead her normal life between attacks, but later ascites, edema and jaundice developed and she died from cholemia. Autopsy confirmed the presence of gross hepatic cirrhosis and splenomegaly. Esophageal varices were present and the portal vein was dilated and showed atheromatous changes. The brain showed no macoscopic or histologic abnormality.

The third case was a female of 20 who had never menstruated. For four years she had had concurrent attacks of diarrhea and water retention lasting up to 3 weeks. She had ascites and edema, but the liver and spleen were impalpable. Finger

clubbing, "liver palms" and spider nevi were, however, present and the liver function tests were those of severe parenchymatous defect, and needle liver biopsy confirmed the presence of hepatic cirrhosis. The blood showed considerable macrocytic anemia. A barium series showed a suggestion of esophageal varices and irregular filling and a "snowstorm" effect in the jejunum. Fat balances showed 87–90 per cent absorption. She was later readmitted febrile and unconscious; her limbs showed clasp knife rigidity, twitching, and athetotic movements; her face was expressionless and her speech slow and monotonous. She recovered spontaneously, but two further attacks of drowsiness and pyrexia have occurred, each episode having been associated with diarrhea and water storage. During attacks, electroencephalography showed a large dominant slow rhythm in all leads with phase reversal at both temporal electrodes, but between attacks the electroencephalographic pattern was normal.

The precise mechanism of these attacks is not understood but they appear to be associated with fluid retention and, though not in themselves dangerous and not requiring any particular treatment, they probably indicate that the disease is nearing a fatal termination.

The abnormal electroencephalographic patterns are probably nonspecific and simply the result of coma. 10 references.—*Author's abstract.*

43. *Urinary 17-Ketosteroids in Chronic Liver Disease.* T. L. WILLIAMS, A. CANTAROW, K. E. PASCHKIS AND W. P. HAVENS, JR., Philadelphia, Pa. Endocrinology *48*:651–57, June 1951.

This study was undertaken for the purpose of securing data on the free and total neutral urinary 17-ketosteroids in normal subjects and patients with chronic hepatic disease before and after a single injection of a relatively large amount of testosterone (167 mg.).

The daily excretion of total 17-ketosteroids was considerably lower in patients with chronic liver disease than in normal subjects. The proportion excreted in the free state was considerably increased. The recovery, as urinary ketosteroids or 167 mg. testosterone, was 12.8 to 59.6 per cent in normal subjects, and 9.5 to 40.9 per cent in those with liver disease. The proportion recovered in the free state was higher in the latter group.

These data suggest that the capacity of the organism, presumably of the liver, for conjugation of metabolites of testosterone is impaired in subjects with chronic liver disease. 18 references. 2 tables.—*Author's abstract.*

44. *The Treatment of External Pancreatic Fistula.* JOSEPH M. MILLER, MILTON GINSBERG AND RAYMOND J. LIPIN, Fort Howard, Md. Postgrad. Med. *10*:31–34, July 1951.

The continued loss of large amounts of sodium through an external pancreatic fistula will produce a characteristic clinical syndrome comprised of profound weakness, fatigue, anorexia, nausea, vomiting, dehydration, loss of weight, and mental lethargy. Accompanying these changes are a decreased concentration of sodium,

chloride and bicarbonate in the serum. The administration of physiologic saline, blood and plasma, the latter two substances to hold sodium in the blood stream, will correct the abnormal state produced by loss of sodium. Since calcium is also lost, it must be replaced. During the period immediately after the establishment of the fistula, the rate of pancreatic secretion and therefore loss through the fistula can be considerably reduced. Since the production of salt and water in pancreatic secretion is governed by the secretion mechanism, which is secondarily dependent upon gastric acidity and motility, a regimen which includes oral starvation and continuous aspiration of the acid contents of the stomach will be helpful. The administration of ephedrine will also decrease the rate of secretion by vasoconstriction in the pancreas. If digestion of the skin occurs, a 1 per cent solution of acetic acid in glycerine is recommended to keep the trypsinogen inactive. A moderately thick suspension of aluminum powder in mineral oil also affords protection. Where secretion is profuse, the irritating fluid can be removed by suction. If this program does not lead to spontaneous closure of the fistula in about two weeks, oral starvation and continuous evacuation of the stomach will have to be abandoned. Continued attention to metabolic balance in the form of intravenous administration of a physiologic solution of sodium chloride and a diet rich in protein and calories will result in closure in many of these instances of chronic fistula. Surgical closure is reserved for the small number of patients who do not respond to these measures or who are unwilling to wait for closure over a prolonged period of time. 10 references.—*Author's abstract.*

45. *The Cause of Fat Necrosis Following Excision of the Pancreatic Duct from Duodenum.* H. L. POPPER AND H. NECHELES, Chicago, Ill. Am. J. Digest. Dis. *18*:293–94, October 1951.

Leaving the excised pancreatic duct, with a piece of duodenum attached to it, freely in the abdomen leads to fat necrosis. The fat necrosis is not due to activation of pancreatic enzymes in the abdominal cavity, but to the prevention of formation of adhesions between omentum or bowel and the flap of duodenal mucosa attached to the duct. This is due to the secretion of enteric fluid and of mucus by the duodenal mucosa. This was proved by experiments in which the pancreatic duct with its attached piece of duodenum was placed under conditions favoring the formation of adhesions. 5 references.—*Author's abstract.*

# genitourinary diseases

46. *Artificial Kidney: Treatment of Acute and Chronic Uremia.* W. J. KOLFF, Cleveland Clin. Quart. *17*:216, July 1950.

All types of artificial kidneys can be divided into four groups: (1) purely dialyzing (Kolff rotating type), (2) purely filtrating type of artificial kidney (Malinow and

Korzon), (3) dialyzing and filtrating (practically all other artificial kidneys), (4) artificial kidneys employing exchange resins. Vivo dialysis can replace all known excretory functions of the kidney. Moreover it can regulate the electrolyte pattern of the blood plasma water, inasmuch as this approaches the composition of the rinsing fluid.

Clinical improvement has been convincing in cases of acute and chronic uremia. The lives of bilaterally nephrectomized dogs have been prolonged to as much as 25 days. In experienced hands, treatment with artificial kidneys imposes little risk. It may be an effective adjunct to other methods of treatment. Congestive heart failure in the presence of uremia may be an additional reason for prompt dialysis. While these statements can be made, it should not be forgotten that two important factors in the treatment of both acute and chronic uremia are the proper regulation of diet and the maintenance of water and electrolyte balance.

47. *Treatment of Uremia; Use and Indications for High Caloric Low Protein Diet, Dialyzing Methods and Replacement Transfusions.* W. J. KOLFF, Cleveland Clin. Quart. *18*:145, July 1951.

In acute anuric uremia restriction of water (700 cc.) and electrolytes (none if not demonstrably lost) is imperative. In the diuretic phase of uremia, clinical judgment and laboratory technics should control water and electrolyte balance if the kidneys are unable to do so. Moderate depression of sodium chloride may be an advantage, since it reduces the blood pressure and diminishes the risk of convulsions and congestive heart failure.

Potassium deficiency is not uncommon in chronic uremia, but in acute anuria hyperpotassemia is a frequent cause of death. The high blood potassium may be reduced by oral administration of potassium-free exchange resins, by forced feeding, or intravenous feeding of carbohydrates in large amounts or, most effectively by dialysis.

The importance of the forced high caloric low or nonprotein diet (Borst) lies in its protein-sparing effect. If the caloric intake is high enough (1600 to 3000 calories per day), very little body protein is catabolized. Consequently little urea is formed (2 to 5 Gm. per 24 hours, while the starving individual will form 12 Gm. in the same time). A hypothetical man with complete anuria could live for 25 days before his blood urea would reach 350 mg. per hundred ml. Practical examples of this diet are presented in the original article. Avoidance of infections with antibiotics also prevents urea production. Operations would greatly increase it and endanger patients.

Most patients do not need more than the previously mentioned conservative measures. If these measures are used, the mortality of acute anuria is not high and patients with chronic uremia seem to live happier and longer. Sometimes the elimination of retention products (and potassium) is indicated. In such cases, the artificial kidney or peritoneal lavage may help a patient through an acute phase of the disease toward recovery or in chronic cases may restore the patient's nitrogen equilibrium. Intestinal dialysis, employing the entire tract, appeared difficult and exhausting to patients in severe clinical condition. Dialysis through an isolated

loop offers a chance to those patients with chronic uremia to whom we can offer nothing else. Replacement transfusions are useful in the restoration of hemoglobin but cumbersome when utilized to combat uremia. Exchange transfusions where the donor receives the patient's blood in turn for his own have had disastrous consequences for the donor. Macrodex is preferred over other blood substitutes, if hypotension has to be treated in patients with uremia.

# musculoskeletal diseases

48. *The Adrenal Cortex in Rheumatic Disease. Pathologic Study with Reference to Effects of Cortisone and Corticotropin.* LEON SOKOLOFF, JOHN T. SHARP AND EDWIN H. KAUFMAN, New York, N. Y. A. M. A. Arch. Int. Med. *88*:627–39, November 1951.

In addition to a careful histologic examination of the adrenal, three types of measurement have been made in the present study: 1) weight, 2) cholesterol content and 3) a quantitative analysis of the zonal architecture.

One hundred and twenty-six cases of various types have been studied by these methods: these include as controls, numbers of healthy individuals dying rather suddenly as a result of trauma: individuals dying of a wide variety of diseases without obvious endocrine dysfunction and without treatment with hormonal preparations; individuals with large, destructive tumors of the anterior lobe of the pituitary. The rheumatic diseases studied were rheumatic fever, rheumatoid arthritis, and disseminated lupus erythematosus. Thirty three individuals had received varying doses of corticotropin (ACTH) or cortisone.

The adrenal cortex in rheumatic diseases has no changes that distinguish it from the adrenal cortex in nonrheumatic disease. Small doses (2000 mg. or less) of ACTH or cortisone do not cause appreciable change. Large doses of ACTH induce marked hypertrophy that apparently regresses after cessation of therapy. Large doses of cortisone sometimes result in atrophy. The cortex is restored to normal size when the medication is discontinued. The adrenal cortex in rheumatic diseases responds in the same manner to ACTH and cortisone as it does in nonrheumatic diseases. Permanent morphologic alteration does not commonly result from the administration of these preparations. 26 references. 6 figures.—*Author's abstract.*

49. *ACTH and Cortisone as Therapeutic Agents in Arthritis and some Locomotor Disorders.* OTTO STEINBROCKER, SIDNEY BERKOWITZ, SOLOMON CARP, MORTIMER EHRLICH, MORTIMER ELKIND, MURRAY SILVER AND NORMAN SPITZER, New York. Bull. N. Y. Acad. Med. *27*:560–76, September 1951.

This is a report of experience with cortisone and ACTH in a study designed to see how effectively and safely these compounds may be applied as therapeutic agents. Of 128 patients, there were 72 with rheumatoid arthritis, 23 with rheumatoid-like arthropathies and 33 with nonrheumatoid musculoskeletal conditions, in the series. All were hospitalized and a preliminary control period using placebos was first employed.

Cortisone and ACTH produced clinically similar results, and the choice depended upon economic considerations and availability at the time. The dosages employed were those in common use except that in slowly responding cases, cortisone was maintained at 200 mg. and ACTH at 80–100 mg. a day until symptoms were adequately resolved, following which a gradual reduction to an effective maintenance dosage was accomplished. Oral cortisone was used in the same dosage as parenteral, but increased by 25 per cent if necessary. During the follow-up periods, there were frequent placebo substitutions without the patients' knowledge for further control observations.

In rheumatoid arthritis, the results followed the well known pattern of impressive over-all relief, but objective standards were used to assess the results according to the Therapeutic Criteria of the American Rheumatism Association. At the end of the initial hospitalization, the results were 4 per cent Grade 1 (complete remission), 40 per cent Grade 2 (greatly improved), 54 per cent Grade 3 (slight improvement) and 2 per cent Grade 4 (none or worse). Of the 72 cases, 35 were followed for periods of 30–340 days. A moderate deterioration of results was observed with lengthened follow-up periods according to the same criteria. These latter results were respectively: 5 per cent, 27 per cent, 51 per cent, and 17 per cent.

Rheumatoid-like diseases consisted of 23 cases. These included ankylosing spondylitis, psoriasis with arthropathy, ulcerative colitis with arthropathy, gout, scleroderma, disseminated lupus erythematosus, and dermatomyositis. The joint symptoms and signs in all of these rheumatoid-like diseases exhibited a pattern of response similar to that of rheumatoid arthritis with the same tendency toward inevitable recurrence when administration of the drugs was stopped. Twelve of the 23 cases showed great and the remainder slight, but definite improvement.

Nonrheumatoid disorders were treated in 34 cases. Of 10 cases of osteoarthritis of the hip, all advanced in degree and unresponsive to previous varied treatment, only one showed significant increase in motion. The other nine, however, experienced relief of pain either complete or marked, and better coordination of motion. Smaller maintenance doses could be used in these conditions except in the quite painful ones.

Ten cases of shoulder-hand syndrome were treated, 9 in the advanced stage. One exhibited complete improvement, 2 great, 2 slight, and 2 none. In 10 cases of periarthritis of the shoulder, 6 showed great improvement, 1 slight, and 3 none in terms of functional improvement. All reported definite to complete relief of pain. In these latter two categories increased doses were required, 200 mg. of cortisone and 75–100 mg. of ACTH. The beneficial action of steroid therapy in these sometimes self-arresting conditions suggests its use in comparatively short periods to accelerate improvement.

One case of acute calcific tendonitis showed complete relief of pain in 24 hours, with marked diminution of severe disability in 3 days. In 1 chronic case of 2 years' duration, tenderness to palpation was greatly improved in 7 days. The calcific deposits in both cases were unchanged after therapy.

A "trigger finger" of long duration was unresponsive in 2 patients.

Side-effects and complications appeared in 40 per cent of the patients, and 90 per cent of these were temporary, quickly reversible, or of no clinical importance. The most serious and troublesome were the vascular accidents, the psychotic reactions, the neuropathies, and the fractures secondary to osteoporosis.

The versatility of cortisone and ACTH is shown by their beneficial effects in these varied arthropathies and locomotor disorders in which the underlying pathologic process may be inflammatory, degenerative, metabolic, irritative, or neurovascular. These compounds produce the most rapid, predictable, and effective suppression of symptoms of any agent so far available in the conditions discussed. In view of the relatively short period of time these potent drugs have been under study, however, and the incompleteness of our information regarding the full range of clinical and pathologic changes, particularly during their long term administration in chronic articular diseases, the definitive evaluation of cortisone and ACTH as practical therapeutic agents must be deferred for the time. 12 references. 5 tables. —*Author's abstract.*

50. *"Experimental Error" of Therapeutic Trials in Rheumatoid Arthritis.* P. D. BEDFORD, Oxford, England. Ann. Rheumat. Dis. *10*:111–15, June 1951.

A study of eight elderly women with chronic rheumatoid arthritis in relapse is reported.

Although no treatment was given, the incidence of hour-by-hour variation in symptoms and signs was high, and the extent of change considerable.

The reasons for these variations are analyzed.

Because of the large "experimental error," the method of serial clinical assessment without statistical control and analysis, is unsuitable for therapeutic trials. 1 reference. 1 figure.—*Author's abstract.*

51. *Osteo-Dental Dysplasia (Cleido-cranial dysostosis). The "Arnold Head."* W. P. U. JACKSON, Cape Town, South Africa. Acta Med. Scandinav. *139*:292–307. f. 4, 1951.

The story of an investigation into a family of "Cape Malays" which contained members affected with osteo-dental dysplasia (cleido-cranial dysostosis) is briefly described. This family was initiated by a Chinese who settled in the Cape and who has so far had 356 direct descendants, at least 70 of whom have been dysplastic. Mention is then made of important publications and summaries describing this condition, an example of which has actually been found in a prehistoric Neanderthal type of skull.

It is evident from the literature and from this family that the developmental defects which characterise osteo-dental dysplasia affect far more than just bones developing from membrane. The permanent teeth — enamel, dentine and root portions, the bones of the face, the sternum, scapulae, vertebrae, pelvic bones, long bones, metacarpals, and phalanges may also show defects. The condition appears to be due to faulty (mainly delayed) development of pre-osseous and pre-dental structures, including both ectodermal and mesodermal tissue. The un-

known causal agent is operative from the fifth week of fetal life for an indefinite period, possibly extending into childhood. The bone which is formed is normal in properties, but enamel and dentine may both be defective. It is evident that the old name "cleido-cranial dysostosis" is inadequate and misleading and should be discarded. It is suggested that "osteo-dental dysplasia" would be more appropriate and more comparable with the related disorder, achondroplasia. It is hoped that others will follow this suggestion and that a name more correctly descriptive than cleido-cranial dysostosis may come into general use in future.

Apart from isolated cases of O.D.D. which have been not infrequently described, analysis of all reported families shows that it is inherited as a dominant characteristic with complete penetrance. A peculiar tendency to passage from the affected parent to like-sexed children was indicated in published figures, but this is not the case with the present family. On the other hand this family shows an unexpected predominance of affected females over males in siblings with an affected parent. This preponderance seems greater than could reasonably be explained by chance and can otherwise only indicate incomplete penetrance of the characteristic to the male sex, although this hypothesis is not in accord with the almost 1:1 ratio of affected to normal siblings (70:73). There has been nothing to suggest that males are apt to be affected to a lesser degree than females and so might be more likely to remain undiagnosed. No evidence of sex-linkage has been discovered in the present family.

From a practical point of view, O.D.D. is usually said to give rise to no disability. The fallacy of this belief is shown by the findings of no single affected member over 20 in this family who had retained any teeth whatever. Other true disabilities are the postural deformities of the spine, coxa vara, genu valgum, talipes, and pes planus, occasional congenital dislocations, and the deformities of the pelvic inlet which may even necessitate cesarean section. Some authors (see Kilgore and Lasker, 1946) have stated that there is a greater tendency for affected children to develop epilepsy (damage to underprotected brain?), and even to die in early infancy. Deafness, speech defects, and mental deficiency have also been reported occasionally.

# neurology and psychiatry

52. *A Case in which Sydenham's Chorea Occurred in Both Mother and Daughter in a 27 Year Interval.* (*Un cas de chorée de Sydenham chez la mère et chez la fille à 27 ans d'intervalle*). M. SCHACHTER, Marseilles, France. Ann. franç. pédiat. *8*:292–95, No. 4, 1951.

The author reports a case in a girl 12 years and 4 months of age, who showed typical symptoms of chorea; a year previously, she had had a similar attack, which lasted about three months. There had been no evidence of rheumatic fever at any time and there was no cardiac involvement. The mother gave a history of a similar attack of chorea at the age of thirteen. The daughter showed a slight enlargement of

the thyroid, but no signs of hyperthyroidism; the mother, however, had definite symptoms of hyperthyroidism and a small goiter. She also had never had any symptoms of rheumatic infection. In both cases the attack of chorea had followed an emotional disturbance. This case is regarded by the author as a hereditary or familial type of Sydenham's chorea; a brief resume of other cases of this type reported in the literature is given. 7 references.

53. *Polysymptomatic Headache.* A. D. JONES, New York, N. Y. Am. Pract. *8*:574–76, July 1951.

A nonanalyzable, poorly organized and inadequate female, 32 years of age, presented incapacitating headaches as her main difficulty. A careful evaluation of her history revealed the presence of three types of headaches. (1) Migraine headache with the typical pulsating pain, localized on the right side. Her age at onset was eleven. Precipitating factors were conscious and unconscious emotional stimuli of sexual nature. Combined ergotamine and caffeine (Cafergone) offered relief. (2) Muscle tension headache characterized by a dull ache over vertex spreading to the occipital region. Her age at onset was 11 years. Precipitating factors were quarrels between mother and father and unexpressed hostility towards her sister. Aspirin alleviated the pain. (3) Allergic or "vacuum" headache manifested by dull annoying pain over the right eye extending to bridge of nose. The patient experienced difficulty in breathing through nose and had nasal speech. It was caused by a secreting disturbance of the nasal mucous membranes. The plugging of the various openings leading to the sinuses created a closed cavity from which the circulating blood would absorb the remaining air. A vacuum would thus be created subjecting the surrounding walls of the sinuses to the pressure of the atmosphere similar to the condition prevailing in the middle ear following rapid descent from great heights. Pain was relieved by diphenhydramine hydrochloride (benadryl). Careful indoctrination of the patient led to the disappearance of her headaches. The placebo effect can be ruled out, since a reversal of the drugs used failed to give relief to the patient. 1 table.—*Author's abstract.*

54. *The Attitude Theory of Emotion.* NINA BULL, Milan, Italy. Arch. psicol., neurol. e psichiat., August 1951.

A new theory of emotion in which preparatory motor attitude is considered as preceding and giving rise to feeling (affect) is shown to have been clearly foreshadowed by Alfred Binet. In a paper called "What is an Emotion?", published shortly before his death, Binet contends that emotions are attitudes, that is, actions in preparation; and that an emotion becomes conscious when the attitude is perceived.

The present concept was formulated without knowledge of Binet's thesis, and stems from, while it alters, the James-Lange-Sergi theory. Its basic claims have been studied extensively in experimental work with hypnotic subjects at the Psychiatric Institute, New York City, and a new method is briefly described whereby specific emotions were induced by means of a stimulus-word denoting an emotion.

Types of body attitude were elicited in this way which corresponded respectively to feelings (as afterwards reported by the subjects) of depression, elation, disgust, fear, and anger. Some samples of these findings are given and interpreted.

A second, differently oriented study of emotion in hypnotic subjects is described by B. Pasquarelli who planned the study and conducted it. This time an attempt was made to disprove the Attitude Theory by demonstrating its inoperability as a working hypothesis. "The method employed was essentially as follows: (1) to suggest in deep hypnotic trance a postural set specific for a given emotion; (2) to lock the subject in that postural set, using the phrase *you are locked*, and prohibiting any changes in the body; and (3) to suggest (directly by a stimulus-word) an emotion at variance with the postural set already induced.

"In all the experiments without exception it was quite impossible to elicit any change in affect without a corresponding change in somatic pattern. It was thus shown that hypnotized subjects could not comply with the suggestion forbidding any changes in posture or bodily sensation if they experienced a new emotion. Any affective shift implicitly included bodily changes, those in the realm of postural set being particularly noticeable."

A correlation of the Attitude Theory with Gemelli's concept of the origin of affective states is pointed up in some detail; and the similarity of a Soviet concept of "Consciousness in Action" is emphasized. It is considered significant that psychologic formulations on the nature of feeling have been published during the past decade in three different countries—Italy, the U.S.S.R. and the U.S.—quite independently of one another, and yet essentially harmonious.

A parallelism has been shown by J. W. Papez to exist between the central mechanism of emotion and the Attitude Theory, which binds, he says, "the anatomical evidence and functional formulations into a coherent whole."

# hematopoietic diseases

55. *The Variable Effects of Identical Amounts of Dicumarol on the Prothrombin Values of Different Persons.* WILLIAM E. WELLMAN AND EDGAR V. ALLEN, Rochester, Minn. Proc. Staff Meet. Mayo Clin. *26*:257–59, July 4, 1951.

The data forming the basis of this study are a part of the records of a large number of patients who received dicumarol. The response of the prothrombin time in different patients to oral administration of the same amount of dicumarol is widely divergent. This study emphasizes the fact that there is no 'dosage of dicumarol, but that use of this anticoagulant must always be based on repeated determinations of the value of prothrombin in the blood. 1 figure.—*Author's abstract.*

# metabolic and endocrine disorders

56. *Use of Desoxycorticosterone Acetate in Dehydration and Malnutrition in Infancy.* JOHN A. BIGLER AND HOWARD S. TRAISMAN, Chicago, Ill. A. M. A. Am. J. Dis. Child. *82*:548–54, November 1951.

Dehydration and malnutrition are frequently seen associated with vomiting and diarrhea in infants. Most patients respond well to parenteral fluids, plasma, blood, and antibiotics. However, occasionally some of these infants are refractory to the standard therapeutic regimes. Ten such patients are described who were treated with desoxycorticosterone acetate and sodium chloride. Two of these infants appeared to represent clinical evidence of adrenal cortical failure.

Jaudon has stated that such temporary adrenal cortical dysfunction can occur during infancy, and that boys are usually affected. Blood chemistry determinations may reveal a normal to depressed sodium and depressed chloride and carbon dioxide combining power. Nonprotein nitrogen and potassium may be elevated.

Of the group of ten patients described, eight were boys. Nine of ten were under six months of age, and one was one year of age.

When improvement took place, it was usually striking. There were cessation of vomiting and diarrhea, and improvement in appetite. The infants became hungry. In all of the patients, there was some evidence of edema, which was slight in all but one case. In this particular infant, treatment was discontinued because of the edema. When desoxycorticosterone acetate and sodium chloride was stopped, there was usually a loss of weight of several ounces within 24 to 48 hours, after which a steady but normal weight gain took place. How much the retention of fluid means in these cases has not been determined. We have administered sodium chloride, 1 to 2 Gm. daily, to a few infants without the addition of desoxycorticosterone acetate and have not had the same results as when the two were combined.

Weight gain and clinical improvement were noted in nine of the ten patients. The one failure was a patient who was markedly dehydrated following a colostomy for agenesis of the myenteric plexus and failed to respond to all therapy. At autopsy of this patient, the agenesis of the myenteric plexus was observed, and the adrenal glands were considered normal.

From our clinical results, further observation of treatment with desoxycorticosterone acetate and sodium chloride may be indicated in malnourished and dehydrated infants who have failed to respond to the standard types of management. It must be emphasized that this is purely an empirical method of treatment. The exact role that the adrenal gland plays in these patients is unknown. Patients receiving desoxycorticosterone acetate should be observed carefully for the development of edema.

57. *Fifty Years of Study of the Role of Protein in Nutrition.* HOWARD B. LEWIS, Ann Arbor, Michigan. Read before the 34th Annual Meeting of the American Dietetic Association, Cleveland, Ohio, October 11, 1951.

At the beginning of the twentieth century, Verworn reiterated Mulder's concept

of primary importance of protein in the living organism with the statement, "The proteins stand at the centre of organic life." At the end of the first half of the current century, despite the increasing importance of studies of enzymes, hormones, minerals and particularly vitamins, the proteins are still "first," and interest in proteins in nutrition is still at a high level. The emphasis has changed from protein as such to a consideration of the importance of the 19 structural elements of protein, the various amino acids, their distribution in the proteins of foodstuffs, through essential or nonessential nature and their individual roles in biologic processes.

Today more than ever, high protein diets are the rule in medical practice. It is the era of higher protein in contrast to 1901–1910, when Chittenden was advocating limitation of dietary protein in his classical work, *Physiological Economy in Nutrition*.

The discussion will be concerned primarily with a consideration of the shift of point of view of the role of protein in nutrition in the first half of the present century and of the experimental studies which led to this.

58. *Studies on the Metabolism of Cardiac Muscle from Animals in Shock.* WALTER J. BURDETTE, New Orleans, La. Yale J. Biol. & Med. 23:505–14, June 1951.

Since cardiac muscle, which plays such an important role in maintaining the circulation, may be affected as well as other tissues by the state of shock, certain aspects of the metabolism of cardiac muscle from shocked animals were studied. Shock was induced by the application of rubber bands to the hind legs followed by release, and in a few experiments, by bleeding from the tail vein over a period of one hour by the method of Sayers, Sayers, and Long. In previous studies, it was shown that oxygen consumption of the muscle increased at first, followed by a significant decrease below normal levels about the fourth hour following treatment. Later there was a secondary rise in $Q_{O_2}$. These relative changes occurred both with and without the addition of sodium pyruvate substrate, although the oxygen uptake was higher when pyruvate was present.

A decrease in glycogen content of significant proportion occurred four hours after release of constrictors accompanied by a suggested increase in lactic acid, and significant elevation in the level of pyruvate acid was evident as early as two hours previous to this time. Sodium iodoacetate caused a depression in $Q_{O_2}$ of slices from rats in shock as well as those without treatment; so systems affected by iodoacetate apparently are functioning at least partially in the stages of shock studied. Reducing the concentration of potassium in the saline medium had no consistent effect on oxygen consumption of the muscle, and therefore no evidence for a relationship between elevated concentration of potassium in the blood and the effect on the myocardium was found. The average R. Q. of slices respiring in saline medium was 0.76 for animals without treatment and 0.71 for those in shock, indicating that other material as well as carbohydrate may be utilized in shock. The changes found could be explained by the effects of reduced oxygen supply on the muscle, but some caution should be exercised in reaching this conclusion.

Undoubtedly shock affects the metabolism of cardiac muscle profoundly, particularly in the later stages, but as a tissue it is not so greatly affected in many re-

spects as the tissue of certain other organs. Whether impairment of the function of the heart as the central organ for maintaining the circulation minimizes the importance of these differences is not clear at the present time, and the feasibility of improving the entire circulatory picture by correcting defects produced by shock is a subject for continued study. 35 references. 5 tables.—*Author's abstract.*

59. *Heredity and Diabetes.* E. M. WATSON AND MARGARET W. THOMPSON, Fort Wayne, Indiana. Am. J. Digest. Dis. *18*:326–30, November 1951.

A positive family history of diabetes mellitus is presented by approximately 50 percent of diabetic patients. Although diabetes thus shows a marked familial tendency, the exact mode of inheritance of the disease, as yet, has not been determined completely, chiefly because of the absence of full concordance between the diabetic genotype and phenotype. Nor has the nature of the inherited proclivity been decided. The percentage of cases with positive family histories of diabetes varies inversely with the age at onset of the disease. The age at onset is earlier in those cases with positive family histories of diabetes than in those without such family histories and is especially early in those with bilateral family histories. On the whole, the available evidence favors the hypothesis that diabetes is inherited as a recessive. The age at onset of the disease is positively correlated in sibs but not, or only slightly, correlated in parent-offspring pairs. There is conflicting evidence as to whether diabetes is more likely to appear in the like-sexed than in the unlike-sexed sibs of diabetic propositi, but the present observations suggest that, if any such relationship exists, it can be explained on the basis of the preponderance of female diabetics. 25 references. 3 tables.—*Author's abstract.*

60. *Care of the Juvenile Diabetic.* GEORGE H. LOWRY, Ann Arbor, Michigan. University of Michigan Med. Bull. *17*:274–81, August 1951.

The care of the juvenile patient with diabetes mellitus must be individualized. The educational program of the patient and his parents is of utmost importance in preventing the development of psychologic problems which may interfere with effective control of the disease. The objectives of this educational program must be aimed at producing a child who has a healthy respect for his disease but who does not live in fear of it. It is important that the physician who cares for these children be sympathetic and patient, and be willing to spend considerable time with them when the diagnosis is first made and upon return visits.

Diet and insulin are so balanced that the danger of either an insulin reaction or acidosis are minimized, and the patient can lead an active and near normal life. A liberal amount of carbohydrate is put in the diet and the likes and dislikes of the child are respected. N P H insulin is used in the majority of cases and has been found very satisfactory in the control of the disease. It is given as a single injection before breakfast. Instruction of the child and his parents should alert them to the signs and symptoms of possible emergencies and their immediate care.

The treatments of the medical emergencies that arise as a complication of diabetes in children are briefly outlined. 8 references.—*Author's abstract.*

61. *Diabetic Coma. Problems of Fluid and Electrolyte Balance.* MARTIN G. GOLDNER, Brooklyn, N. Y. Am. J. Digest. Dis. *18*:235–40, August 1951.

The author emphasizes those problems which are of particular interest to the practicing physician: a) extent of the disturbances in fluid and electrolyte balance in diabetic coma, b) cause, c) treatment and prevention. First, a correlation is attempted between the clinical signs and symptoms and the accompanying biochemical changes in the body fluids of the diabetic patient elapsing into coma. Next, the etiologic role of hyperglycemia in precipitating these signs, symptoms and biochemical changes is discussed and it is pointed out that the determining etiological factor is a critical degree of insulin deficiency and not the hyperglycemia *per se*. Following, the vicious circle is described by which various clinical conditions as gastrointestinal diseases, endocrine disorders, trauma (surgery), inflammations, etc. cause dehydration—starvation—ketogenesis—electrolyte loss—acidosis and finally coma. In the discussion of therapy, emphasis is given both to insulin as the most essential means to stop water loss, ketogenesis and acidosis, and to the need for fluid as replacement as well as to combat circulatory shock. Hypopotassemia and hypoglycemia are mentioned as possible dangerous side effects of insulin and the indications are given for safe potassium and glucose administration. 2 figures. 1 table.—*Author's abstract.*

62. *Streptokinase and Streptodornase in the Treatment of Diabetic Gangrene.* LEON V. MCVAY JR., AND DOUGLAS H. SPRUNT, Memphis, Tenn. A. M. A. Archives of Internal Medicine *87*:551–93, April 1951.

Gangrene is one of the most common and serious complications of diabetes mellitus. The preferred treatment of the condition is its prevention. This involves the early diagnosis of diabetes and the subsequent use of a proper insulin and dietary regimen. Of primary importance is the thorough education of each patient concerning the care of the lower extremities.

Following the actual development of diabetic gangrene, immediate therapeutic action is necessary. All cases should be under the observation of both internist and surgeon. It must be emphasized that amputation is not always necessary. If the gangrenous area is superficial and demarcated with adequate circulation, nonoperative therapy is justified. However, if a satisfactory response is not obtained, surgical intervention is indicated as soon as possible. Operation is often impossible. Frequently surgical therapy is refused by the patient. Often a life of semi-invalidism is preferred to amputation. Furthermore, the patient's physical condition may contraindicate surgery.

Because of the underlying vascular pathology, advances in the conservative treatment of diabetic gangrene have not been striking. After a consideration of the unsatisfactory status of nonoperative therapy, we investigated the effectiveness of streptokinase and streptodornase, two enzyme preparations obtained from the hemolytic streptococci. In three cases of diabetic gangrene, the results were excellent. There was rapid relief of pain and epithelization of the involved area. In another instance, conservative therapy was initially regarded as futile inasmuch as two ulcerations had been present (with only brief periods of improvement) for 32 years.

Nevertheless, in six months progress was sufficient to warrant the surgical service recommending plastic repair. In the fifth case, extensive and painful radiation necrosis occurred in a senile diabetic. Epithelization and relief of pain followed local therapy with streptokinase, streptodornase and aureomycin.

In all but one case, streptokinase and streptodornase were combined with aureomycin powder to give a liquid which shortly after application formed a semipaste. This removed the necessity for surgical dressings, was comfortable, and controlled or prevented secondary infection. The local application of these enzyme preparations with, or without, aureomycin is simple. Therefore, treatment may be carried out at home by the patient or by his family. In no instance were toxic reactions to streptokinase and streptodornase noted.

It appears that streptokinase and streptodornase are of great value in the conservative treatment of diabetic gangrene. 5 figures.—*Author's abstract.*

63. *Intercapillary Glomerulosclerosis.* M. IVERSEN & A. SOEBORG OHLSEN, Gentofte, Denmark. Acta Med. Scandinav. *139*:319–25. f. 4, 1951.

The writers report 7 cases of intercapillary glomerulosclerosis found in an examination of the autopsy records of diabetics who died during the period from January 1946 to January 1949 in the three medical departments of the Copenhagen County Hospital at Gentofte. Mention is made of the pathology and clinical picture of the disease.

64. *Spermatogenesis and Apparent Fertility in Eunuchoid Male in Eleventh Year of Androgen Therapy.* S. C. WERNER, New York, N. Y. J. Clin. Endo. *11*:612–20, June 1951.

The evidence for the achievement of spermatogenesis and fertility in a eunuchoid male in the tenth and eleventh years of treatment with androgens is detailed. The results of semen counts, testicular biopsy, and blood groupings are presented. 10 references. 4 figures. 3 tables.—*Author's abstract.*

65. *Hemodilution as a Result of Estrogen Therapy. Estrogenic Effects in the Human Female.* CARROLL L. WITTEN AND JAMES T. BRADBURY, Louisville, Ky. Proc. Soc. Exper. Biol. and Med. *72*:626–29, November 1951.

Following a review of the literature on the blood changes associated with estrogen therapy, the authors state that they believed it might be of value to determine the effects of estrogen on the blood of human females in the hope that some correlation with the vasomotor symptoms of the postmenopausal syndrome might be discovered. Also with the current widespread use of this treatment, it would be of interest to ascertain the effect of the ovarian hormone on extragenital tissues. The patients included in this study were 16 women suffering from minor menstrual irregularities between the ages of 15 and 52 years. In the younger patients, the blood studies were made during the intermenstrual period. The estrogen dose consisted either of 5 mg. theelin (estrone) or 0.4 mg. of $\alpha$-estradiol propionate per in-

jection. The blood volume was determined in 3 patients. Red cell counts, hemoglobin, hematocrit composition, and blood volume were determined.

In all 16 patients, there was a lowering of the erythrocyte count, hemoglobin and hematocrit during 4 to 10 days of estrogen therapy. On cessation of the treatment, these substances returned to their initial levels after 5 to 8 days. The blood volume determined in 3 patients increased sufficiently to explain the reduction in the red blood cell count, hemoglobin and hematocrit.

During the short period of estrogen therapy there may be considerable hemodilution. Further studies will be required to determine whether this effect is transitory or may be maintained indefinitely. Loss of blood volume following oophorectomy and corrected by estrogen therapy suggests that the vasomotor symptoms of the surgical or natural menopause may be in part a reflection of the blood volume changes. Hemodilution in pregnancy also suggests the possibility that the increased estrogen level during pregnancy may be a causative factor of the increased blood volume in the "physiological anemia" of pregnancy. A study of premenstrual edema would be of interest to determine whether an intravascular fluid increase parallels the extravascular fluid increase. Hematologic studies during treatment with estrogen and progesterone or testosterone would show whether these hormones modify or augment the action of the estrogens. 10 references. 5 figures. 1 table.

66. *The Determination of Sulfhydryl Groups in Serum. II. Protein Alterations Associated with Disease.* EMANUEL B. SCHOENBACH, NORMAN WEISSMAN, AND ELEANOR B. ARMISTEAD, Baltimore, Md. J. Clin. Invest. *30*:762–77, July 1951.

Studies of serum proteins both in health and in disease were made in the hope that knowledge as to the pathogenesis of a number of diseases might be obtained. The protein content was determined after ammonium sulfate fractionation, methanol separation, and electrophoretic analysis into the albumin and various globulin components. The sulfhydryl content of the total serum proteins as well as of the albumin-globulin components was also determined employing the amperometric technique.

Initial studies showed that normal individuals had 44–45 micromoles of sulfhydryl per gram protein nitrogen; in the albumin fractions the content was 63–64, while the globulin was 23–24. In patients with carcinoma, leukemia, infections, degenerative diseases, etc., the sulfhydryl content of the serum protein was found to be significantly reduced.

A more extensive study was made on selected individuals in whom the protein was characterized as to its nitrogen, biuret, and sulfhydryl content, as well as by serial electrophoretic studies.

Patients with malignancy showed reduction in their albumin content with a more marked reduction in the sulfhydryl content. The ratio of peptide to nitrogen content was within the normal range. Similar observations were made on patients with multiple myeloma. Among this group it was noted that the micromoles of albumin sulfhydryl were reduced far below normal in all, and nondetectible in one case. The sulfhydryl of the globulin nitrogen despite the marked increase in glo-

bulin content was usually below normal, although in two individuals a high normal value was obtained. There was no difference among sera with a high content of M-protein or gamma-globulin.

In patients with lupus erythematosus, the sulfhydryl again was reduced even when corrected for the reduction in the albumin protein content and the increase in globulin fractions. Studies were also made on patients with rheumatoid arthritis, glomerulonephritis, hemochromatosis, cirrhosis, leukemia, and cystinuria.

The effect of ACTH and cortisone therapy was observed among patients with rheumatoid arthritis and lupus erythematosus, in whom, despite a shift in the protein content to a more normal distribution of albumin-globulin components, the sulfhydryl valuation did not reflect a parallel change. In patients with malignancy who were treated with the folic acid antagonists and in whom a remission occurred, the sulfhydryl values per unit of protein nitrogen or per peptide unit approached normal.

These studies indicate that, during many pathologic states, abnormality in protein formation occurs, which is sharply delineated by measuring the sulfhydryl content. The reduction in the albumin component with normal or increased globulin was consistently observed in the sera of these patients, but the peptide per milligram of protein nitrogen did not deviate markedly from the normal. The sulfhydryl per milligram of protein nitrogen or per peptide bond was subnormal in both albumin and globulin components. These abnormalities are graphically presented. Further investigations into the metabolic abnormalities related to the abnormal synthesis of protein are suggested. 21 references. 12 figures. 6 tables.—*Author's abstract*

# geriatrics

67. *Endocrine Patterns During Aging.* THOMAS HODGE MCGAVACK, New York, N. Y. Ann. Int. Med. *35*:961–74, November 1951.

Histologic changes in the endocrine glands during aging vary markedly from species to species. In the gonad, there is a thinning of the epithelium and of smooth muscle. In the pituitary, there is a slightly progressive increase in the reticular fibres of the sinusoidal capillaries with a decrease in cellular elements and vacuolization of the basophilic cells. In the adrenal, there is a gradual conversion of reticulum into collagen, most marked in the reticular and least noticeable in the fascicular zone. In the thyroid, there is a decrease in the size of the follicles with atrophy of the epithelium and an increase in interacinar connective tissue. These changes are not dissimilar from the long-term effects consequent upon ablation of the gonad. In 76 subjects who were normally aging, the excretion of urinary gonadotrophins and 17-ketosteroid gradually decreased with increase in years. High values for gonadotrophins were observed at the menopause in the majority of women. In 104 subjects suffering from the climacterium, 53 percent showed a variation from standard values in the excretion of 17-ketosteroids and 37 percent a variation in the basal metabolic rate. There was little alteration in the urinary output of 11-oxy-

corticoids. Alterations of probable significance were observed for (a) the excretion of 11-oxycorticoids and 17-ketosteroids in diabetes mellitus, the Achard-Thiers syndrome and osteoporosis, and (b) the response to administered DCA and salt in arthritis and hypertension. For this study, patients were selected in whom the clinical manifestations of illness occurred during or following the climacteric. The possible endocrine relationships existing in normally and abnormally aging subjects are discussed, and the fact that many conditioning factors play a part in normal and abnormal aging is stressed. 60 references. 4 figures. 2 tables.—*Author's abstract.*

# dermatology and syphilology

68. *Occurrence of Skin Pigmentation During Mesantoin Therapy.* HARRIOT HUNTER AND DALTON JENKINS, Denver, Colo. J. A. M. A. *147*:744–48, October 20, 1951.

This paper reports six cases of epilepsy currently under treatment with Mesantoin, all of whom showed a peculiar identical pigmentation of the skin of the face and neck. Six case histories were presented in some detail. The possibility that this pigmentation is due to Mesantoin is discussed. The pigmentation in question is described as a patchy brownish or "bronze" discoloration appearing over the face and neck around the hairline, and in one case, over the arms. It appeared rather insidiously and escaped the notice of several observers until they were specifically instructed to look for it. All cases were studied for possible etiologic factors other than Mesantoin toxicity, but no such causation could be found. Tests for adrenal insufficiency were conclusively negative. Biopsy showed the pigment to be melanin, but was otherwise unremarkable. No other signs of Mesantoin toxicity were noted in any of the patients. Mesantoin was discontinued in one patient because of clinical improvement, and the skin virtually cleared to its normal status. This was taken as presumptive evidence that Mesantoin was the causative agent in the production of the pigmentation, but so far there is no explanation of the mechanism involved. 2 references. 7 figures.—*Author's abstract.*

69. *Chronic Urticaria Following Penicillin Therapy.* ERVIN EPSTEIN, Oakland, Calif. California Med. *74*:429–30, June 1951.

Urticaria developed in 6 patients 3 to 10 days after the intramuscular injection of penicillin, and the condition persisted for from 3 to 15 months. The suffering, disability, and expense that resulted from the injection indicates that physicians should make certain that the patient who receives penicillin has a true indication for its use. The complication led to mental depression in half of the cases. In only 2 of the cases was there an incontestable indication for penicillin therapy (pneumonia and syphilis), the others receiving it for bronchitis, wound prophylaxis, and after dental extraction. At the time the report was written, all 6 patients still had urticaria.—*Author's abstract.*

70. *Investigations in a Case of Urticaria Pigmentosa.* J. M. DRENNAN, J. MARTIN BEARE, London, Eng. Brit. J. Derm. *63*:257–61, July 1951.

A typical case of urticaria pigmentosa in a boy of 12 was used to test the value of certain drugs and chemicals which theoretically might be useful in treating this disease. (1) Those of proved value in the treatment of ordinary urticaria; Antistin (.005 per cent), adrenal ne (.001 per cent), novocaine (1 per cent). (2) The heparin antagonists, toluidine blue (.1 per cent) and protamine sulphate (1 per cent), which were given with the idea of neutralizing the heparin secreted by the mast cells in the skin lesions.

These substances in the concentrations given, dissolved where necessary in .5 cc. normal saline, were injected into localized skin lesions, which were then stimulated by gentle rubbing. The usual urticarial reaction, unmodified by treatment, developed in every case.

The oral and intravenous routes were used in two other experiments: (1) a four week's course of Anthisan was given, the dosage being .5 Gm. by mouth three times daily; (2) 250 cc. of a .15 per cent solution of toluidine blue in normal saline sterilized by filtration was run into a vein over a period of 45 minutes. The subsequent response of the skin lesions to gentle rubbing was again unaltered.

This investigation suggests that neither heparin nor histamine are responsible for the clinical manifestations which may perhaps be due to other, unidentified substances liberated from the mast cells in this disease. 14 references.—*Author's abstract.*

71. *Primary Herpes Simplex Virus Infection of the Adult with a Note on the Relation of Herpes Simplex Virus to Recurrent Aphthous Stomatitis.* EDWIN D. KILBOURNE AND FRANK L. HORSFALL JR., New York, N. Y. A. M. A. Arch. Int. Med. *88*:195–96, October 1951.

Infection of man with the virus of herpes simplex commonly occurs in infancy when it is usually manifest as an acute stomatitis. This primary infantile infection is followed by the latent persistence of virus in the tissues. At times the latent virus may be activated and induce mild recurrent disease in the form of vesicular lesions of the lips or other sites invaded during the primary infection. In the majority of adults, serologic evidence indicates previous infection with herpes simplex virus.

Primary herpetic infection of the adult has been only rarely described. Essential to this diagnosis is the demonstration of specific neutralization or complement-fixing antibodies during convalescence, but not in the acute phase of the illness. Presentation is made of two cases of febrile illness in adults associated with the recovery of herpes simplex virus from throat washings and the demonstration of specific neutralizing antibodies in convalescent serum, but not in acute phase serum. In both patients the clinical syndrome was reminiscent of infectious mononucleosis although heterophile agglutinations were negative. In one patient, a 42 year old white male, the illness was characterized by a paucity of localizing symptoms and signs and was mainly characterized by malaise, epigastric burning, facial pares-

thesia, and low grade fever. In the case of the second patient, a 21 year old white male, the predominant features were symptoms and signs of an acute pharyngitis associated with high fever.

The recovery of virus and the demonstration of antibody response in both instances was accomplished by the intraperitoneal inoculation of infant mice. Data are presented suggesting a greater susceptibility to herpes simplex virus of the infant mouse than the more commonly employed chick embryo.

Study of a third patient subject to recurrent lip vesicles and aphthous ulcers of the mouth and gums resulted in the recovery of herpes simplex virus from aphthous ulcers on three separate occasions suggesting, that this virus may be causally related to recurrent aphthous ulcers.

An extensive review of the literature has disclosed twenty-two additional instances of serologically proved primary herpes simplex virus infection of adults. The clinical states associated with these infections have been protean in nature, ranging from a mild stomatitis to acute inflammation of the brain and meninges. 22 references, 3 figures.—*Author's abstract.*

# book review

*Tumors of the Skin, Benign and Malignant*, Second Edition, JOSEPH JORDAN ELLER AND WILLIAM DOUGLAS ELLER, Philadelphia, Lea and Febiger, 1951.

The field of neoplasia has been widened extensively in the past few years and the many individual systems involved can no longer be covered with any degree of facility in a general textbook. For this reason alone, the work by Eller and Eller, which confines itself to benign and malignant tumors of the skin, should prove to be a welcome addition to the medical library.

The book is well organized and deals with tumors originating in connective, nerve and epithelial tissues, tumors of infectious origin, precancerous conditions, as well as malignant tumors of the skin. There are chapters on sarcoma and the lymphomas, and the section on malignant melanoma is very ably presented. The photographs are plentiful and effective. The pathologic discussions are concise and in many instances illustrated by section material. A chapter on radiation physics is given in great detail.

There is not much to be said, however, from the viewpoint of therapy which, aside from surgery and x-ray, is treated rather meagerly. Of course, very little in the form of specific therapy is available in many of the affections under discussion.

This type of book, therefore, because of its organization and the adequate reference material, is recommended to the dermatologist and the general practitioner

who is interested in the dermal manifestations of benign and malignant neoplasia. However, it cannot be considered encyclopedic and some of the details of radiotherapy and surgical procedure could well have been omitted. It would perhaps have been more valuable to have assembled data on the comparative effectiveness of therapeutic regimens rather than to have outlined the various types of therapy employed, especially since the latter for the most part are too specialized.—*Emanuel B. Schoenbach, M.D.*

## Francis Gilman Blake, M. D.

It is indeed with regret that we record the demise of Dr. Francis Gilman Blake who has served for many years on the Editorial Board of the QUARTERLY REVIEW OF MEDICINE.

Dr. Blake was an outstanding authority in both investigative work and in teaching. As professor of medicine and dean of the Yale Medical School, his influence upon the development of physicians will long be remembered, especially to those students who had the opportunity to be under his tutelage. His contributions to measles, pneumonia, superinfection and chemotherapy have been of fundamental significance.

During the war Dr. Blake was Chairman of the Army Epidemiological Board and, in addition to outstanding organizational and administrative capacities, he showed the spirit of the true investigator by organizing and himself participating in the field investigations of scrub typhus in New Guinea. He contracted malaria while undertaking this investigation under the auspices of the army. For his distinguished service, Dr. Blake was awarded the Medal of Merit from the Secretary of War.

From 1948 to 1951, in addition to his work at Yale as Sterling Professor of Medicine, he was Chairman of the Division of Medical Sciences of the Research and Development Board in the Department of Defense.

Dr. Blake was a member of many outstanding scientific organizations and served with conscientious devotion on many boards and committees.

He died at the age of 65 on February 1, 1952 of a cardiovascular ailment.—*Emanuel B. Schoenbach, M.D.*

# Quarterly Review of Internal Medicine and Dermatology

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